CASE REPORT

Resection of liver metastasis derived from alpha-fetoprotein-producing gastric cancer—report of 4 cases

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Received: 28 May 2015 / Accepted: 19 August 2015 / Published online: 4 September 2015
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Abstract As is the case for metastatic liver tumors derived from standard gastric cancers, there is no consensus about the optimal treatment for metastatic liver tumors derived from alpha-fetoprotein (AFP)-producing gastric cancer, including regarding the surgical indications for such lesions. We report the cases of 4 patients in whom metastatic liver tumors derived from AFP-producing gastric cancer that were curatively resected. One of the patients had a thrombus in his inferior vena cava at the time of the liver resection, and both the liver tumor and thrombus were completely removed. The patient has survived 93 months after receiving multidisciplinary therapy including partial pneumonectomy, chemotherapy, and radiotherapy and currently has no evaluable disease. Another patient has survived for 3 years without suffering any recurrence. Since long-term survival is possible, liver resection should be considered as a treatment for liver metastases from AFP-producing gastric cancers.

Keywords Alpha-fetoprotein-producing gastric cancer · Liver metastasis · Metastatic liver tumor · Hepatectomy

Introduction

Alpha-fetoprotein (AFP)-producing gastric cancer (APGC) accounts for 1–6 % of all gastric cancers [1], and the 5-year survival rate is reported to range from 8.3 to 41 %

[2–6], which is inferior to that of standard gastric cancer (GC) [6]. Liver metastasis (LM) occurs in 60.6 % of APGCs [6], which is considered to contribute to the poor prognosis of the condition.

The optimal treatments for liver metastases (LMs) derived from standard GC or APGC remain to be determined. There have been several reports about the surgical treatment of LMs derived from standard GC [7, 8]; however, there have only been a few reports about the surgical treatment of LMs derived from APGC. We report 4 cases of LMs derived from APGC receiving hepatectomy in our department (Table 1).

Case 1

A 60-year-old man was admitted to another hospital with bleeding from a GC with a LM. Total gastrectomy (D2) was performed emergently. According to the Japanese Classification of Gastric Cancer [9], the pathological findings were pT1 ≥ T2, med, INFB, ly1, v0, T2 (MP), N1, stage IV. The LM was treated with TS-1 (80 mg/day). The patient experienced right upper abdominal pain at 9 postoperative months, and a blood test detected a high concentration of AFP (69,600 ng/ml). Contrast-enhanced computed tomography (CT) depicted a 25-cm tumor covering most of the right hepatic lobe and some of the medial segment of the liver with tumor embolus in the inferior vena cava (Fig. 1a). Immunohistochemical staining of the primary GC was found to be positive for AFP. The patient had been referred to our department and right trisectionectomy, removal of the tumor embolus, and cholecystectomy were performed (Fig. 1b). The hepatic tumor was demonstrated to be a hepatoid adenocarcinoma resembling a GC. Immunohistochemical examination was found to be

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Table 1 Clinicopathological features of 4 cases

Case	1	2	3	4
Age	60	70	70	80
Sex	Male	Male	Male	Male
Stage of gastric cancer	Stage IV	Stage II	Stage IV	Stage IB
Timing of liver metastasis	Synchronous	Metachronous	Synchronous	Metachronous
AFP (ng/ml) levels at liver metastasis	69,600	476.5	120,900	29,100.7
AFP immunohistochemical staining for gastric cancer	Positive	Positive	Positive	NA
AFP immunohistochemical staining for liver tumor	Positive	Negative	Positive	Positive
Size (cm) of liver metastasis	25	7	8.5 6.5	10
Number of liver metastasis	1	1	2	1
Type of liver resection	Right trisectionectomy	Anterior sectionectomy	Left lobectomy, partial resection	Partial resection
Adjuvant chemotherapy after liver resection	TS-1, CDDP, CPT-11	None	5-FU, UFT	UFT
Recurrence sites	Lung, hilar lymph node	None	Peritoneum	Lung
Treatment for recurrence	Resection (lung), radiation (lymph node)	None	5-FU, UFT	UFT
Prognosis	93 months alive with no tumor	36 months alive with no tumor	16 months died	51 months alive with tumor

NA not assessment

Fig. 1 a CT image of case 1. A tumor measuring 25 cm covered most of the right hepatic lobe and some of the medial segment of the liver. A tumor embolus was detected in the inferior vena cava. **b** Resection of the tumor in case 1. Right hepatic trisegmentectomy and cholecystectomy were performed, and the tumor embolus was removed

positive for AFP (Fig. 2), and the liver tumor was diagnosed as a LM derived from APGC. The tumor had not invaded the serosa. Tumor emboli were found in the peripheral portal, right hepatic, and middle hepatic veins. TS-1 was continued, and the serum AFP level decreased to 2366 ng/ml at 2 months after the hepatectomy (Fig. 3). Serum AFP level had increased again at 4 months after the hepatectomy and metastatic tumors in his right lung was detected. The treatment was changed to combined chemotherapy involving TS-1 (50 mg/day) and cisplatin (CDDP 60 mg/m²), and the serum AFP level had decreased

to 499 ng/ml. However, CDDP could not be continued because the patient was malnourished, and serum AFP level started to rise again. At 18 months after the hepatectomy, right hilar lymph node metastasis was detected and it was treated with external-beam radiotherapy involving a total dose of 60 Gy delivered in 24 fractions. The chemotherapy was replaced with irinotecan (CPT-11 100 mg/body) plus CDDP (50 mg/body) and right hilar lymph node metastasis disappeared. At 34 and 45 months after the hepatectomy, partial resection of the left lung and right lung was performed with video-assisted thoracic

Fig. 2 Microscopic images of the liver tumor demonstrated that it was a hepatoid adenocarcinoma and was positive for AFP staining (**a** H&E stain, original magnification: $\times 20$; **b** AFP stain, original magnification: $\times 20$)

Fig. 3 Clinical course including the serum AFP levels of the patient in case 1. Multidisciplinary therapy including partial pneumonectomy, chemotherapy, and radiotherapy were successful, and the patient was disease-free and displayed normal serum AFP levels at 93 months after the liver resection

surgery (VATS). The serum AFP level remained normal after surgery, and CPT-11 plus CDDP was discontinued at 78 months after the hepatectomy. There was no evaluable disease at 93 months after the hepatectomy.

Case 2

A 70-year-old man with a medical history of total gastrectomy for APGC was referred to our department with a LM. A pathological examination of the GC were ly1, v2, T2 (SS), N1, stage II [9] and immunohistochemical staining of the tumor cells for AFP produced a positive result. A high serum level of AFP (476.5 ng/ml) was detected at 68

postoperative months, and CT imaging demonstrated a tumor measuring 7 cm in S8 of the liver. A right anterior sectionectomy was performed at our department. A pathological examination of the liver tumor demonstrated that it was a metastatic GC, but immunohistochemical staining of the hepatic tumor cells for AFP produced a negative result. The patient's serum AFP level normalized after the surgery. There were no signs of recurrence at 36 months after the hepatectomy, without any adjuvant therapy.

Case 3

A 70-year-old man had been previously admitted to another hospital with general malaise due to anemia. Patient was diagnosed as GC and two liver tumors were detected. Tumor in his left hepatic lobe was 8.5 cm and another tumor in S5/6 was 6.5 cm. The patient's serum AFP and carcinoembryonic antigen (CEA) levels were 120,900 and 9.7 ng/ml, respectively. He was referred to our department and distal gastrectomy, left hepatectomy, partial resection of S5/6 of the liver, and cholecystectomy were performed. The pathological findings were APGC (hepatoid adenocarcinoma), ly2, v3, T2 (SS), N2 [9] with LMs. Immunohistochemical examinations demonstrated that both the gastric and LMs were positive for AFP. After the surgery, Forty mg epirubicin was infused through the right hepatic artery and uracil-tegafur (UFT 300 mg/day) and a weekly infusion of 5-fluorouracil (500 mg/body) were followed. Recurrence was detected along the medial abdominal incision at 12 postoperative months. The patient died at the 16th postoperative month.

Table 2 Liver metastases from AFP-producing gastric treated with hepatectomy

Reference no.	Age	Sex	Timing of liver metastasis	Maximum tumor size (cm)	Number of tumors	Liver resection process	Serum AFP (ng/ml)	Adjuvant chemotherapy	Recurrence sites	Prognosis
[27]	58	Male	Synchronous	0.2	1	Partial resection	91.3	UFT, CDDP, Mitomycin, Etoposide	None	More than 100 days with no tumor
[28]	61	Female	Synchronous	Not mentioned	1	Posterior segmentectomy	910	None	None	More than 1 year with no tumor
[29]	68	Male	Metachronous	2.8	2	Partial resection	301	None	None	12 months with no tumor
[33]	57	Male	Metachronous	3	1	Partial resection	140	5-FU	None	3 years with no tumor
[30]	71	Male	Synchronous	3.2	3	Partial resection, extended posterior sectionectomy	5960	None	Liver	6 months died
[32]	67	Male	Metachronous	3.5	1	Left hepatectomy	281.5	UFT	Remnant stomach	11 years with no tumor
[24]	70	Male	Metachronous	Not mentioned	2	Right hepatectomy	Not mentioned	None	Liver, peritoneum	1 year 5 months died
[31]	78	Male	Synchronous	6	1	Partial resection	2260	None	Liver	11 M died
Case 1	60	Male	Synchronous	25	1	Right trisectionectomy	69,600	TS-1, CDDP, CPT-11	Lung, hilar lymph node	93 months with no tumor
Case 2	70	Male	Metachronous	7	1	Anterior sectionectomy	476.5	None	None	36 months with no tumor
Case 3	70	Male	Synchronous	8.5	2	Left hepatectomy, partial resection	120,900	5-FU, UFT	Peritoneum	16 months died
Case 4	80	Male	Metachronous	10	1	Partial resection	29,100.7	UFT	Lung	51 months with tumor

Case 4

An 80-year-old man with a medical history of distal gastrectomy (D2) for GC and diagnosed with a LM derived from GC was referred to our department. The GC exhibited the following pathological findings: tub2, int, INF β , ly1, v1, T2, N0, stage IB [9]. Immunohistochemical staining for AFP was not performed. A tumor measuring 10 cm was detected in S6/7 of the liver at 21 months after the gastrectomy. The patient's serum AFP level was 29,100.7 ng/ml. Partial resection of the liver was performed. A pathological examination of the liver tumor demonstrated metastasis from GC, and immunohistochemical staining for AFP was positive. UFT was administered orally for adjuvant chemotherapy. Although the patient's serum AFP level remained normal, multiple lung metastases were detected at 41 months after the hepatectomy. Fifty-one months have passed since the hepatectomy, and the patient is being followed up without any active treatment for recurrent disease.

Discussion

5-year survival rate of APGC are reported to range from 8.3 to 41 % [2–6], showing more aggressive behavior and poorer prognosis than standard GCs [6]. Hirajima et al. [10] have reported that the prognosis of APGCs without LM was similar to the prognosis of standard GCs and suggested that the high incidence of the LMs (60.6 %) [6] contributes to the poor prognosis of APGC. In their report, 5-year survival rate of APGC patients who develop LMs was 0 % [10]. Early APGC has the same tendency for LM as advanced APGC [11]. The exact mechanism that contributes to the aggressive behavior of APGC is still not clear. Some authors suggested overexpression of c-Met receptor, receptor that regulates cell proliferation and migration, was frequently observed in APGC and is associated with higher frequency of distant metastasis including LM [12, 13]. Other sites of distant metastasis include lung, distant lymph node [14], pancreas [15], brain [16], tentorium cerebelli [17], and adrenal gland [18].

There is no definitive therapeutic strategy for LMs derived from APGC, and some case reports with systemic chemotherapy [19–21], hepatic artery infusion chemotherapy [22, 23], radiation therapy [24], transcatheter arterial embolization [22], and hepatectomy exist. Some effectively treated previous case reports involved follow-up periods of less than 3 years [25, 26]. Also, some cases of LMs treated with hepatectomy have been reported with short follow-up period [27–29] or suggested that patients exhibit a poor prognosis after hepatectomy [2, 24,

30, 31]. Few reports have involved patients that survived for long periods. One case report described a patient who survived for 11 years [32], and another involved a patient who survived for 3 years after hepatectomy [33]. Neither of these patients had any residual tumor. These reported cases of LMs from APGC treated with hepatectomy are described in Table 2, with present reported cases. The report by Kono et al. [5] included 3 cases in which solitary LM from APGC was curatively resected, and one of these patients survived for more than 3 years.

Considering the past reports of hepatectomy of LMs derived from APGCs, there are not enough reports to conclude the effect of hepatectomy in the whole treatment strategy, and more reports discussing hepatectomy are needed. Present report includes 4 such cases with long follow-up. One of these patients has survived for 93 months after receiving multidisciplinary therapy after the hepatectomy and has no evaluable disease at present. Another patient has survived for 3 years without suffering any recurrence without any adjuvant chemotherapy.

Since LMs contributes to the poor prognosis of APGC, effective strategy to treat LMs needs to be established. Learning from our cases, hepatectomy with adjuvant chemotherapy should be considered as a treatment for metachronous or synchronous LMs from APGCs if the complete resection can be achieved. In particular, when LM was completely removed as Case 1, local treatments as resection and radiation for lymph node metastases and lung metastases might be effective for long-term survival. In conclusion, more reports are needed to evaluate the effect of hepatectomy of LMs from APGC; however, since long-term survival is possible, hepatectomy with adjuvant chemotherapy should be considered as a treatment for LMs from APGCs if the complete resection can be achieved.

Compliance with ethical standards

All the analysis in this study was performed in accordance with ethical guidelines of Hokkaido University Hospital. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors. Identifying information about participants is not available in the article.

Conflict of interest The authors declare that they have no conflict of interest.

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