Case Report
Metachronous Liver Metastasis from Alpha-Fetoprotein-Producing Gastric Cancer Successfully Treated with Capecitabine/Oxaliplatin Combination Chemotherapy

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1. Introduction
Alpha-fetoprotein- (AFP-) producing gastric carcinomas account for approximately 1.3–15% of all gastric cancers [1]. These carcinomas are associated with a higher rate of liver metastasis and poorer prognosis (5-year survival rate, 8–28%) than AFP-negative (ordinal) gastric carcinomas [1–4]. The clinicopathological characteristics and molecular mechanisms of AFP-producing gastric carcinomas are not fully understood due to their rarity. As a result, there is currently a lack of consensus for a standard therapeutic policy for AFP-producing gastric carcinomas, including cases with metachronous liver metastasis.

Several studies that have investigated AFP-producing gastric carcinomas over the past several decades have reported unsatisfactory outcomes following the curative resection of the primary tumor or liver metastasis. However, some reports have suggested that multimodal therapies, including surgery, other regional treatment, and chemotherapy, may be effective in improving patient prognosis [5]. We herein report a case of metachronous liver metastasis from AFP-producing gastric carcinoma after curative gastrectomy. This was successfully treated with capecitabine/oxaliplatin (CapeOX) combination chemotherapy.

2. Case Report
A 73-year-old man with anemia was referred to the Department of Gastroenterology of our hospital. He had a positive fecal occult blood test and high serum AFP level, but no history...
of liver cirrhosis or hepatitis. Blood tests indicated hemoglobin, serum AFP, serum carcinoembryonic antigen, and serum carbohydrate antigen 19-9 levels of 8.4 g/dL (reference range, 13.5–18.0 g/dL), 207.7 ng/mL (reference range, 0.0–10.0 ng/mL), 45.8 ng/mL (reference range, 0.0–5.0 ng/mL), and 11 U/mL (reference range, 0–37 U/mL), respectively. Upper gastrointestinal endoscopy revealed an 11 × 5 cm semicircular Bormann type 2 tumor on the greater curvature of the gastric corpus that extended to the pylorus (Figure 1(a)). A biopsy of the tumor showed a well to moderately differentiated adenocarcinoma. The wall of the distal stomach was thickened on contrast-enhanced computed tomography (CE-CT); no signs of ascites, lymph node metastasis, remote metastasis, or tumor invasion was noted in the pancreas (Figure 1(b)). CE-CT and gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) confirmed the absence of a liver tumor.

The patient underwent an open total gastrectomy, lymphadenectomy, and Roux-en-Y reconstruction for gastric adenocarcinoma. The histopathological diagnosis was primary gastric cancer (pT2, pN2, M0, and stage IIB (Union for International Cancer Control TNM Classification of Malignant Tumors, 8th edition)) (d, e). Immunostaining of the primary tumor was positive for alpha-fetoprotein and negative for human epidermal growth factor receptor 2 (f, g, respectively).
Tumors, 8th edition)) (Figures 1(c)–1(e)). Immunostaining of the primary tumor was positive for AFP and negative for human epidermal growth factor receptor 2 (Figures 1(f) and 1(g)). The patient was treated with eight cycles of S-1 monotherapy (tegafur/gimeracil/oteracil) (120 mg/day on days 1–14, every 3 weeks) as an adjuvant chemotherapy. Serum AFP levels decreased to 3.5 ng/mL (Figure 2), and no recurrence was observed on blood tests every 3 months and CE-CT every 6 months over the 3-year surveillance period. However, serum AFP levels started to increase up to 19.6 ng/mL, 3.5 years after curative gastrectomy (Figure 2). CE-CT revealed a hypovascular nodule in segment 5/6 of the liver (Figures 3(a) and 3(b)). A 9 mm nodule was observed on T1- and T2-weighted MRI; this nodule was categorized as a defect on EOB-MRI (Figures 3(c)–3(e)). Positron emission tomography with 2-deoxy-2-[18F]fluoro-D-glucose integrated with computed tomography ([18F]-FDG PET/CT) showed an abnormal accumulation of [18F]-fluordeoxyglucose (FDG) (maximum standardized uptake value of 4.8) at the same point (Figure 3(f)). Recurrent liver metastasis from an AFP-producing gastric carcinoma was diagnosed, and the patient subsequently underwent four cycles of CapeOX combination chemotherapy (capcitabine, 3000 mg/day on days 1–14, every 3 weeks; oxaliplatin, 130 mg/m² on day 1, every 3 weeks). No remarkable side effects occurred during the dosing period. The tumor was not detected on CE-CT, EOB-MRI, or contrast-enhanced ultrasonography using perflubutane (CE-US) following treatment; no accumulation of [18F]-FDG was observed by [18F]-FDG PET/CT (Figures 3(g) and 3(h)). The level of serum AFP decreased to within the normal range (5.6 ng/mL) (Figure 2). No recurrence was detected at 1.5-year follow-up.

3. Discussion

We described a case of metachronous liver metastasis from AFP-producing gastric carcinoma after curative gastrectomy, which resulted in complete resolution of the tumor with CapeOX combination chemotherapy without performing hepatic resection. To the best of our knowledge, no prior studies in the English and Japanese literature have reported the successful treatment of metachronous liver metastasis from AFP-producing gastric carcinoma with CapeOX combination chemotherapy. The association between primary gastric carcinoma and both high serum AFP levels and liver metastasis was first reported by Bourreille et al. in 1970 [6]. Even early stage AFP-producing gastric carcinomas may be associated with multiple liver metastasis and mortality within a couple of years after curative gastrectomy [7]. Compared to noncurative gastrectomy, curative-intent gastrectomy may improve the 5-year survival rate from 3–42% and the mean survival period from 9–29 months in patients with AFP-producing gastric carcinoma [8]. However, the lower 5-year survival rate in patients with AFP-producing gastric carcinoma compared to those with ordinal gastric carcinoma (5-year survival rate of approximately 70% [3]) suggests that surgery alone may not be adequate for early stage AFP-producing gastric carcinoma.

While a previous study reported the long-term survival of a patient with AFP-producing gastric carcinoma who was treated with an oral derivative of 5-fluorouracil (S-1) monotherapy (a standard postoperative regimen for ordinal gastric carcinoma) [9], our case showed that combined curative gastrectomy and adjuvant S-1 monotherapy were unable to prevent metachronous liver metastasis. A wide range of chemotherapeutic regimens and local treatments have been identified as potentially effective for advanced or recurrent AFP-producing gastric carcinomas; some have been able to achieve complete tumor resolution in the target region or long-term disease-free survival (Table 1) [9–21]. CapeOX combination therapy has been generally administered in cases of gastrointestinal malignancy as a neoadjuvant or conversion therapy; some studies have reported successful treatment outcomes (Table 2) [22–26]. Despite absence of successful treatment of recurrent liver metastasis from AFP-producing gastric carcinoma, we selected CapeOX combination therapy for tumor demonstrating resistance to S-1 monotherapy with reference to a previous report on unresectable AFP-producing hepatoid adenocarcinoma of peritoneum and omentum successfully treated by CapeOX combination therapy [27]. The reason CapeOX combination therapy successfully treated metachronous liver metastasis in the present case is unknown; however, CapeOX combination therapy may have the same potential in treating AFP-producing gastric carcinomas as reported in an in vivo study on metastatic colorectal cancer tissue [28], in which the upregulation of thymidine phosphorylase by oxaliplatin might have enhanced the antitumor effect of capcitabine.

According to the latest therapeutic guidelines for metastatic liver tumors, hepatectomy is performed if metachronous liver metastasis from ordinal gastric carcinoma meets the following criteria: (1) R0 resection is achievable, (2) three or fewer in number, (3) smaller than 3–5 cm in size, and (4) disease-free period of >2 years after the initial gastrectomy [29]. While metachronous liver metastasis in the present case satisfied these criteria, we proceeded to administer CapeOX combination therapy with the aim of reducing the risk of
Figure 3: Radiological findings following liver metastasis (segment 5/6) from AFP-producing gastric carcinoma contrast-enhanced computed tomography revealing a hypovascular nodule in segment 5/6 of the liver (a, b). T1- and T2-weighted MRI showing a low-signal nodule and slightly high signal, respectively; a 9 mm defect is observed with EOB-MRI (c–e). 18F-FDG PET/CT showing an abnormal accumulation of 18F-FDG (maximum standardized uptake value of 4.8) at the same point (f). The tumor was undetectable on EOB-MRI after four courses of CapeOX therapy; no accumulation was detected on PET/CT (g, h). Abbreviations: CapeOX: capecitabine/oxaliplatin; CT: computed tomography; EOB: gadolinium ethoxybenzyl-diethylenetriaminepentaacetate acid; MRI: magnetic resonance imaging; PET: positron emission tomography; 18F-FDG: 2-deoxy-2-[fluorine-18] fluoro-D-glucose.
| Author                  | Target lesion                                                                 | Treatment                  | Chemotherapy regimen                                      | Outcome                                                                 |
|-------------------------|--------------------------------------------------------------------------------|----------------------------|------------------------------------------------------------|-------------------------------------------------------------------------|
| Sakurai et al. [10]     | Metachronous liver metastasis Portal vein tumor emboli                          | HAI                        | HAI – FU + ADM + MMC with UFT (oral)                       | Alive (disease-free) at 4 years after HAIC                               |
| Takahashi et al. [11]   | Synchronous liver metastasis                                                    | Palliative chemotherapy    | 5 – FU + LV + ETP + CDDP (FLEP)                            | CR                                                                       |
|                         | Primary GC                                                                     | TG                         | ACT: FLEP and S-1                                         | Alive at 7 years after gastrectomy                                      |
| Tsuji et al. [12]       | Primary GC, lymph node metastasis                                                | NAC                        | DOC + S – 1 + CDDP                                        | PR                                                                       |
| Amano et al. [13]       | Primary GC (HER2 positive) cancerous peritonitis                               | Palliative chemotherapy    | Tratuzumab + DOC + S – 1                                  | PR after 8 cycles                                                       |
| Nishiwada et al. [14]   | Primary GC (HER2 positive)                                                       | Palliative chemotherapy    | Tratuzumab + S – 1 + CDDP,                                | Alive at 8 months after chemotherapy initiation (PR)                    |
|                         | synchronous liver metastases                                                    | Radiation                  | HAI – CDDP + S – 1 (oral)                                 | PR                                                                       |
|                         | Metachronous lung metastases                                                   | Palliative chemotherapy    | PTX, DFUR + DOC + CDDP, 5 – FU + ADM + MMC                | Transient CR                                                            |
|                         | Metachronous lung metastases para-aortic lymph node metastasis                  | Palliative chemotherapy    | Sorafenib                                                  | PD at 54 months after gastrectomy                                       |
|                         |                                                                 |                             |                                                            | Dead at 60 months after the initial gastrectomy (PR for 2 months and SD for 4 months) |
| Sun et al. [16]         | Primary GC massive lymph node metastases                                      | Palliative chemotherapy    | 5 – FU + I – OHP + LV, PTX + Capecitabine, S – 1 + I – OHP | PR > gastrectomy                                                        |
|                         |                                                                 |                             |                                                            | Alive at 2 months after gastrectomy (disease-free)                    |
| Watanabe et al. [17]    | Liver/lung metastasis                                                          | Palliative chemotherapy    | S – 1 + CDDP (SP), IRI + CDDP                              | Dead at 15 months after hepatectomy                                      |
| Akamaru et al. [18]     | Primary GC liver metastasis                                                     | DG + lateral hepatectomy    | ACT: S – 1 + CDDP (SP)                                    | Alive at 5.5 years after gastrectomy                                     |
| Doi et al. [19]         | Synchronous liver metastases                                                   | TACE, HAIC                 | HAIC – 5 – FU + CDDP                                      | PD                                                                       |
|                         |                                                                 | Palliative chemotherapy    | CDDP + capectabine                                         | Alive at 2 years after recurrence                                      |
|                         |                                                                 |                             | PTX + RAM                                                  | Alive at 10 years after SP therapy                                      |
| Author                  | Target lesion          | Treatment                          | Chemotherapy regimen                  | Outcome                          |
|------------------------|------------------------|------------------------------------|---------------------------------------|----------------------------------|
| Yasuda et al. [9] (Japanese) | Primary GC            | DG and ACT                         | ACT: S-1                              | Alive at 5 years after gastrectomy |
| Ding and Ding [21]     | Primary GC (HER2 positive) | Palliative chemotherapy             | S-1 + 1-OHP + trastuzumab, DOC + trastuzumab | PD                              |
|                        |                        |                                    | Apatinib                              | PR                               |

Abbreviations: ACT: adjuvant chemotherapy; ADM: adriamycin; AFP: alpha-fetoprotein; CapeOX: capecitabine/oxaliplatin; CDDP: cisplatin; CR: complete response; DFUR: deoxy-5-fluorouridine; DG: distal gastrectomy; DOC: docetaxel; ETP: etoposide; FLEP: 5-fluorouracil/cisplatin; GC: gastric carcinoma; HAI: hepatic arterial injection; HAIC: hepatic artery injection chemotherapy; HER2: human epidermal growth factor receptor 2; IRE: irinotecan; LV: leucovorin; MMC: mitomycin; NAC: neoadjuvant chemotherapy; PD: progressive disease; PR: partial response; PTX: paclitaxel; RAM: ramucirumab; SD: stable disease; SP: tegafur/gimeracil/oteracil and cisplatin; S-1: tegafur/gimeracil/oteracil; TACE: transcatheter arterial chemoembolization; TG: total gastrectomy; UFT: tegafur/uracil; l-OHP: oxaliplatin; 5-FU: 5-fluorouracil. Abbreviations: cited studies, [9–21].
Table 2: Summary of previous reports on AFP-producing gastric carcinomas treated with CapeOX combination therapy. The literature review included studies that were published between January 2001 and November 2021. English language articles were searched on the PubMed/MEDLINE database using the terms “hepatoid adenocarcinoma” or “alpha-fetoprotein-producing adenocarcinoma, capecitabine, and oxaliplatin.” A Japanese literature search was conducted using the ICHUSHI (Igaku Chuo Zasshi) database from the Japan Medical Abstracts Society (JAMAS).

| Author          | Aim of CapeOX      | Primary gastric tumor                                      | Liver metastasis     | Therapeutic effect                                                                 | Outcome                                                                 |
|-----------------|--------------------|-----------------------------------------------------------|----------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Kripp et al. [22] | Palliative         | Esophago-gastric junction carcinoma                       | Synchronous multiple | Long-lasting major remission                                                       | Deceased at 18.5 months                                                  |
| Mori et al. [23] (Japanese) | Conversion         | AFPGC and rectal cancer                                   | Synchronous multiple | (1) CapeOX therapy<br> (2) DG + LAR + partial hepatectomy<br> ACT: not performed<br> (1) PTX + LV + 5-FU<br> (2) Capecitabine<br> (3) TACE – 1-OHP + S – 1 (oral)<br> (4) 5-FU + LV + IRI<br> (5) CapeOX (1 cycle)<br> (6) Sorafenib (oral)<br> (7) nabPTX | Alive at 29 months (disease-free)                                      |
| Fang et al. [24]  | Palliative         | AFPGC                                                     | Synchronous multiple | Deceased at 30 months after diagnosis due to cholestatic jaundice                   |                                                                          |
| Shen et al. [25]   | Neo-adjuvant       | AFPGC with infiltration into left liver lobe and lymphadenectomy | None                 | Alive at 7 months after surgery                                                    |                                                                          |
| Choi et al. [26]   | Palliative (recurrent liver metastasis) | Gastric adenocarcinoma with AFP-positive endodermal sinus tumor component | Metachronous         | Deceased at 11 months after BEP<br> Overall survival: 22 months (mortality due to pneumonia) |                                                                          |

Abbreviations: ACT: adjuvant chemotherapy; AFP: alpha-fetoprotein; AFPGC: alpha-fetoprotein-producing gastric carcinoma; BEP: bleomycin, etoposide, and cisplatin; CapeOX: capecitabine/oxaliplatin; DG: distal gastrectomy; IRI: irinotecan; LAR: low anterior resection; LV: leucovorin; PTX: paclitaxel; S-1: tegafur/gimeracil/oteracil; TACE: transcatheter arterial chemoembolization; 1-OHP: oxaliplatin; nabPTX: nanoparticle albumin-bound paclitaxel; 5-FU, 5-fluourouracil. Abbreviations cited studies. [22–26].
postoperative micrometastatic lesions from AFP-producing gastric carcinoma. Fortunately, no metastatic liver tumors have been undetectable on CE-US or PET/CT after chemotherapy, and there have been no signs of recurrence over a 1.5-year surveillance period. Follow-up for the detection of tumor regrowth is ongoing.

Reports on the successful treatment of metachronous liver metastasis from AFP-producing gastric carcinoma with CapeOX chemotherapy in the English and Japanese literature are lacking. At present, there is limited option but to base the use of chemotherapy regimens on guidelines established for ordinal gastric carcinoma [9]. Since AFP-producing gastric carcinoma, which have biological characteristics that are relatively different from those of AFP-producing gastric carcinoma, is a rare subgroup with poor prognosis, we showed the possibility of the useful preoperative option of CapeOX chemotherapy. Additional studies are required to confirm the effectiveness of pre-surgical CapeOX combination therapy in patients with metachronous liver metastasis from AFP-producing gastric carcinoma.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this journal.

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