Long-term survival of 11 years with multidisciplinary therapy for hepatocellular carcinoma metastasis to the ovary and peritoneum: a case report

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Abstract

We herein report a rare case of HCC metastases to the ovary and peritoneum in a 61-year-old female patient who has achieved 11-year survival with multidisciplinary therapy. The patient was diagnosed with HCC during balloon angioplasty performed for Budd–Chiari syndrome in 1994 and underwent partial hepatectomy twice. Five years after the second hepatectomy, allochronic recurrence of a single nodule detected in S8 was treated by radiofrequency ablation, followed by percutaneous ethanol injection therapy and stereotactic body radiotherapy. However, her α-fetoprotein level rose to 1862 ng/mL within one year and computed tomography revealed a large pelvic tumor suggesting HCC metastasis to the ovary. The subsequent laparotomy revealed one 11-cm left ovarian tumor, one small right ovarian nodule, and numerous peritoneal nodules. Bilateral salpingo-oophorectomy and peritoneal resection of as many nodules as possible were performed. Combination therapy with intravenous 5-fluorouracil plus cisplatin and ramucirumab monotherapy effectively suppressed tumor progression with maintenance of hepatic functional reserve, and she has achieved long-term survival of 11 years, illustrating that multidisciplinary therapy with favorable hepatic functional reserve maintenance can contribute to long-term survival in HCC with extrahepatic spread.

Keywords Hepatocellular carcinoma · Ovary · Peritoneum · Multidisciplinary therapy · Case report

Introduction

The lungs, lymph nodes, bones, and adrenal glands are the most common metastatic sites, and the reported median survival after the diagnosis of extrahepatic spread is 8.1 months [1]. Importantly, the prognosis remains poor in these patients despite the recently developed molecular-targeted agents. We herein report the case of a patient with rare ovarian and peritoneal metastases of HCC who achieved 11-year survival by longitudinal multidisciplinary therapy, which afforded effective maintenance of hepatic functional reserve.

Case report

A 61-year-old female patient was diagnosed with liver cirrhosis due to Budd–Chiari syndrome and underwent balloon angioplasty in 1994. At the time, she was also diagnosed with HCC located in S7 and underwent partial hepatectomy one month later. Eight years after the
initial HCC diagnosis, two new HCC nodules found in S2 and S3 were removed by partial heptectomy as curative surgery. Five years after the second heptectomy, she experienced another HCC recurrence in S8, which presented as corona-like enhancement in computed tomography (CT) images during hepatic arteriography (Fig. 1). Although sequential treatment with radiofrequency ablation (RFA) and percutaneous ethanol injection therapy (PEIT) was performed, local recurrence was detected seven months after the treatment. The patient underwent RFA again. As a result, a liver abscess was developed at the ablation site. After the resolution of abscess with antibiotic treatment, remnant HCC was visualized. Stereotactic body radiotherapy was performed as additional treatment eleven months after the second RFA.

However, her α-fetoprotein (AFP) level reached 1862 ng/mL ten months after stereotactic body radiotherapy (about 2.5 years later from diagnosis of S8 nodule). Neither CT nor magnetic resonance imaging (MRI) showed HCC recurrence in the liver or the upper abdomen, but gynecological examination performed to diagnose lower abdominal discomfort led to the identification of a non-tender, hard mass in the lower abdomen.

The results of laboratory tests performed at the time are presented in Table 1. The levels of AFP and des-γ-carboxy prothrombin (DCP) were elevated (2156 ng/mL and 2302 mAU/mL, respectively), whereas CA125 was slightly above the normal limit (123 U/mL). Her hepatic functional reserve was Child–Pugh A (6 points), and she was in modified albumin-bilirubin (mALBI) grade 2a (score, −2.45). Her renal function was not impaired. MRI indicated a large tumor measuring 11 × 10 × 6 cm in the pelvic cavity (Fig. 2a–d), and the ovary was considered as the origin of the tumor, which was hypervascular and included necrotic areas. No HCC recurrence was detected in the liver by dynamic CT and MRI. No tumor was observed in lymph nodes, lungs, bones, and adrenal glands. Endoscopy did not show any tumors in esophagus, stomach, duodenum, and colon. The pelvic tumor was strongly suspected to be an HCC metastasis based on the patient’s medical history, high levels of AFP and DCP, and no evidence of tumors in other organs.

Bilateral salpingo-oophorectomy as curative therapy was attempted in December 2009. However, in addition to the large ovarian tumor, numerous small nodules in the peritoneum and mesentery were detected

![Fig. 1](image)

**Fig. 1** Computed tomography images during angiography at the time of S8 nodule diagnosis in 2007. a Computed tomography (CT) during arteriopaintography image showing a defect in the portal supply to the tumor. b, c CT during right hepatic arteriography images showing overt enhancement followed by corona-like enhancement, a typical presentation of hepatocellular carcinoma

| Table 1 Laboratory findings at the time of ovarian tumor diagnosis |
|----------------------|-----------------|-----------------|
| TP                   | 7.9 g/dL        | AFP             |
| Alb                  | 3.8 g/dL        | 2156 ng/mL      |
| T-Bil                | 0.9 mg/dL       | DCP             |
| AST                  | 50 U/L          | 2302 mAU/mL     |
| ALT                  | 22 U/L          | CA125           |
| BUN                  | 20 mg/dL        | 123 U/mL        |
| Cre                  | 0.54 mg/dL      | CA19-9          |
| NH3                  | 113 μg/dL       | 5.1 ng/mL       |
| PLT                  | 19.6 × 10^4/μL  | Encephalopathy  |
| PT                   | 85 %            | None            |
| PT-INR               | 1.09            | Mild            |
|                      |                 | Child–Pugh A (6)|
|                      |                 | mALBI grade 2a (−2.45) |
|                      |                 | FIB-4 index 3.32 |
during laparotomy, and as many disseminated nodules as possible were resected in addition to bilateral salpingo-oophorectomy.

Pathological evaluation revealed a yellow solid tumor in the left ovary, 11 × 10 × 6 cm in size, with hemorrhagic and cystic components, partially with aggregations of small nodules (Fig. 3). A nodule, 1.3 × 0.9 cm in size, was detected in the right ovary. Microscopic evaluation showed similar findings in both ovarian tumors, which exhibited alveolar, trabecular, and tubular patterns and comprised eosinophilic cells with a high nuclear/cytoplasm ratio. Immunohistochemical examination showed that the tumors were extensively positive for CAM5.2, partially positive for Hep-Par1 (Fig. 4c) and CK7 (Fig. 4d), and negative for CK20 and AE1/AE3 (data
Peritoneal nodules, ranging from 0.2 to 1 cm in size, exhibited findings similar to those of the ovarian tumors. These findings were compatible with HCC. Based on the medical history and pathological findings, the ovarian and peritoneal tumors were diagnosed as HCC metastases. As a result of the surgery, remnant lesions were located only in the peritoneum because peritoneal resection could not remove all metastatic nodules. AFP decreased to 136 ng/mL.

Two months after bilateral salpingo-oophorectomy, sorafenib (600 mg/day) was initiated as systemic therapy but was withdrawn after 12 days because of severe hand-foot syndrome, which was equivalent to grade 3 in common terminology criteria for adverse events version 5.0. Starting in September 2010, 5-fluorouracil-based regimens, such as an intravenous 5-fluorouracil plus cisplatin (low-dose FP; 5-fluorouracil, 250 mg/body, days 1–5, 8–12, and 15–19 and cisplatin, 10 mg/body, days 1–5, 8–12, and 15–19), and tegafur/gimeracil/oteracil (S-1, 60 mg/day) monotherapy were administered. Although the regimens suppressed an increase of AFP level under 250 ng/mL for a year, a new intrahepatic lesion was detected in September 2012. On-demand transarterial chemoembolization (TACE) was added as locoregional therapy. In March 2015, the patient developed anaphylactic reaction to iodine-containing contrast

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**Fig. 4** Representative microscopic images of the left ovarian tumor. a, b Hematoxylin–eosin staining. Eosinophilic cells with high nuclear/cytoplasm ratio propagate in a compact pattern. c Cells positive for Hep-Par1 are heterogeneously detected in the tumor. d CK7-positive cells forming glandular structures are partly observed in the tumor.

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**Fig. 5** Clinical course during multidisciplinary therapy. Solid and dotted lines show changes in serum alpha-fetoprotein (AFP) levels (ng/mL) and modified albumin-bilirubin score, respectively, during the course of multidisciplinary therapy. 5-FU 5-fluorouracil, LFP intravenous low-dose 5-FU and cisplatin, S-1 tegafur/gimeracil/oteracil, FAIT Fluorouracil arterial infusion and interferon therapy, UFT tegafur/uracil, SOR sorafenib, RAM ramucirumab, RFA radiofrequency ablation, PEIT percutaneous ethanol injection therapy, SBRT stereotactic body radiation therapy, TACE transarterial chemoembolization.
medium, leading to the contraindication of TACE and contrast-enhanced CT; therefore, the patient was treated with 5-fluorouracil-based regimens, such as intravenous 5-fluorouracil plus interferon α-2a, and tegafur/uracil monotherapy. However, long-term tumor suppression was not possible, and transient reduction in hepatic functional reserve was observed. Renal function also started to decline from this period. Because estimated glomerular filtration rate decreased to 56.05 mL/min/1.73m², low-dose sorafenib (200 mg/day) was administered as an alternative treatment and the severity of adverse effects, such as hand-foot syndrome and anorexia, were grade 2 and tolerable. However, the AFP level increased to 5096 ng/mL. Lenvatinib (4 mg), which was initiated as the next treatment, had to be discontinued at day 11 due to a reduction in estimated glomerular filtration rate from 41.01 to 29.31 mL/min/1.73m². After the discontinuation, renal function returned to the former level. The subsequent re-initiation of intravenous low-dose FP with 30% dose of cisplatin could suppress tumor progression until 2018, as shown in Figs. 5 and 6.

In 2019, four hepatic lesions were newly detected by plain CT and contrast-enhanced ultrasound. Percutaneous ethanol injection therapy for the intrahepatic nodule in S5, which grew more rapidly compared to the other three nodules, was followed by ramucirumab monotherapy. Although the treatment was briefly interrupted due to ophthalmic surgery and proteinuria, her AFP level transiently decreased from 4717 to 2418 ng/mL. With the sequential treatment, the patient has been able to maintain improved quality of life and good performance status for 11 years after the initial diagnosis of HCC metastases to the ovary and peritoneum. Because her mALBI score has exhibited only a slight increase from −2.45 to −2.30 despite the long-term treatment, multidisciplinary treatment has been ongoing.

Discussion

Ovarian involvement is extremely rare in HCC. To date, only 16 living cases of HCC metastasis to the ovary have been reported except the present case (Table 2) [2–15]. The first two cases were reported in 1983 by Nakashima et al., who reported one case (0.4%) in an autopsy cohort of 232 HCC cases [16], and by Oortman et al., who reported a living patient [2]. The median age of these reported cases is 44 (range 27–76) years. Unilateral and bilateral involvement was observed in 9 and 8 patients, respectively, and 8 of the 17 cases had peritoneal metastasis.

In patients with HCC metastasis to the ovary, hepatoid yolk sac tumor and primary hepatoid carcinoma of the ovary, both AFP-producing ovarian tumors, should be considered in differential diagnosis. Hepatoid yolk sac tumor is commonly reported in young female patients, with rare occurrence reported in postmenopausal women [17]. Hepatoid carcinoma of the ovary is an uncommon ovarian tumor, first reported in 1987 [18]. The morphological and immunohistochemical features of hepatoid carcinoma of the ovary resemble those of HCC [19–21]. In the present case, the pathological findings were compatible to HCC. Furthermore, the postmenopausal age, history of radiofrequency ablation therapy and percutaneous ethanol injection therapy which can cause ovarian and peritoneal involvement [3, 22], and no evidence of tumors in other organs strongly supported the diagnosis of HCC metastasis to the ovary.

Prognosis of HCC with extrahepatic spread is poor. A meta-analysis reported that 1-year survival rate was 25% in the advanced stage of Barcelona clinic liver cancer staging system [23], and the reported median survival time of extrahepatic spread is approximately 8 months [1, 24]. Ovarian metastases tend to be detected after they become large and exhibit peritoneal involvement, as shown in Table 2, and regular pelvic examination might be essential in patients with HCC, especially after RFA and PEIT. In the present case, it could be retrospectively assumed that the ovarian metastasis emerged in the duration between the second RFA and stereotactic body radiotherapy, when sufficient investigation of the pelvic cavity was not performed. Continuous increase of AFP after the second RFA might reflect the ovarian metastasis. Actually, AFP reflected progression of peritoneal dissemination and intrahepatic lesions after the salpingo-oophorectomy. Several studies reported that radical or palliative surgery of extrahepatic sites could significantly prolong survival in patients with good tumor control in the liver and other organs [3, 4, 12, 25]. Some studies described that surgical resection of peritoneal metastasis could also prolong survival in cases with selected conditions, such as small number of peritoneal nodules, AFP level of less than 200 ng/mL, Child–Pugh A, and well-controlled intrahepatic lesion [26–28]. The median survival time of the reported cases of HCC with ovarian metastasis is 12 months (range 4–54), whereas longer survival times beyond 12 months are expected in patients with previously visible HCC lesions across the body that disappear after surgery.
therapy [37–39], and molecular-targeted therapy [40–43].

...cance of hepatic functional reserve in achieving pro-
...tained during multidisciplinary therapy. The signifi-
...o at least sorafenib-refractory HCC [34].

...did not statistically improve overall survival in patients
...S-1 interferon α. Monotherapy of S-1 was also tried, based on
...arterial 5-fluorouracil-based regimens with cisplatin or
...ous reports [30–32] that described the efficacy of intra-
...route as an alternative therapy, according to the previ-
...did not have tolerability to sorafenib, and the duration
...sorafenib was selected as the first treat-
...sorafenib after recovery from surgical wound as
...resection of the large ovarian tumor might have
...effectiveness of 5-fluorouracil-based regimens to
...peritoneal nodules, sorafenib was selected as the first treat-
...remnant lesions after the salpingo-oophorectomy were located at the
...resection of the large ovarian tumor might have significantly reduced the HCC bulk in the body. Sec-
...leakage was avoided due to allergic reaction. Before percutaneous
...of low-dose sorafenib in 2016 (e, f, g), a new disseminated lesion appeared near the spleen. Use of the contrast
...medium was avoided due to allergic reaction. Before percutaneous
...alan injection therapy (PEIT) in 2019, another intrahepatic lesion in S5 was clarified even in plain CT (h). The lesions of the abdominal
dissemination were stable (i, j). After PEIT in 2020, The intrahepatic
...include low density area which allowed to suggest necro-
...us was only 12 days. The 5-fluorouracil-based regimens were administered from the venous
...progression in patients with unresectable advanced HCC [29]. Therefore, it was decided that the present case
...case did not have tolerability to sorafenib, and the duration
...treatment with maintenance of hepatic functional reserve
...sions. Low-dose FP was administered approximately
...mination and an intrahepatic lesion in S5.

...The present case has survived for 11 years after bilat-
eral salpingo-oophorectomy. We propose that three
...major factors contributed to the prolonged survival with
...quality of life in the present case. First, sur-
gical resection of the large ovarian tumor might have
...effectiveness of 5-fluorouracil-based regimens to
...sorafenib was effective in prolonging median survival and time
...to progress in patients with unresectable advanced

...800 ng/mL, although the adverse effects were
...erumab compared to regorafenib and cabozantinib [47]. In the present case, ramucirumab did

...not decrease tumor volume but dramatically reduced AFP
...and good tolerance even in elderly patients was also reported
...good tolerance even in elderly patients was also reported

...long-term survival of 11 years with improved quality of life and good performance status in a patient with
...due to favorable maintenance of hepatic functional reserve.
Table 2 Summary of 16 reported cases of HCC metastasis to ovaries

| Case | Age | Previous treatment | Tumor characteristics | Location of viable lesion at surgery | Treatment | Other treatment | Prognosis after SO | Report | Year | Ref |
|------|-----|-------------------|----------------------|-------------------------------------|-----------|----------------|------------------|--------|------|-----|
|      |     | Hepatic surgery   | Maximum size of ovary | Liver | Other organs | Ovarian site | Salpingo- | Other | after SO | [months] | |
|      |     | Puncture or rupture | [cm] | | | | ooophorectomy | | | | |
| 1    | 36  | Hepatectomy       | 6 | 18,800 | – | – | Left | Bilateral SO (with TAH) | N/A | 1983 | 2 |
| 2    | 38  | – – | 4–11** | 14,819 | – | – | Left | Bilateral SO (with TAH) | Cx* | – | 52 | 1992 | 4 |
| 3    | 47  | Liver transplantation | – | 20 | 4 | – | Right | Bilateral SO | Radiation to bone meta | 12 | 2000 | 5 |
| 4    | 43  | Hepatectomy | RFA | TACE | 7 | 336,520 | – | – | Right | Right SO | – | N/A | 2011 | 6 |
| 5    | 44  | – – | RFA | – | 7 | 2.8 | – | – | Right | Bilateral SO | – | – | 2017 | 3 |
| 6    | 44  | Liver transplantation | – | 11 | 58 | – | – | Bilateral | Bilateral SO (sirolimus) | – | 14 alive cancer free | 2005 | 8 |
| 7    | 27  | Hepatectomy | RFA | TACE | 3.2 | N/A | – | – | Bilateral | Bilateral SO | – | N/A | 2017 | 7 |
| 8    | 31  | – – | 4–11** | 2700 | Multiple* | – | – | Bilateral | Bilateral SO | Cx* | 18 | 1992 | 4 |
| 9    | 66  | – Biopsy | – | 17 | 55 | Multiple | – | – | Bilateral | Bilateral SO | – | 6 | 1994 | 9 |
| 10   | 61  | – PEIT | – | N/A | 350,000 | N/A | – | Right | Bilateral SO (with TAH) | N/A | N/A | 2001 | 10 |
| 11   | 39  | – – | TACE, Cx* | N/A | 60,000 < | – | – | Lung, spleen, lymph node | Right | N/A | Cx* | N/A | 2004 | 11 (Korean) |
| 12   | 68  | – – | – | 4–11** | 11,000 | single | Peritoneum, lymph node | Bilateral | Bilateral SO, omentectomy | Cisplatin | 5 alive | 1992 | 4 |
| 13   | 76  | Hepatectomy with ileocecal resection due to adhesion | TACE, SOR | ~2.5 | – | Single | Peritoneum | Left | Left SO, hepatectomy | SOR cisplatin (to lung meta) | ~32 alive cancer free | 2013 | 12 (Japanese) |
| 14   | 43  | – – | – | 6.5 | 140 | Multiple | Peritoneum | Left | Left SO, hepatectomy | SOR cisplatin (to lung meta) | ~32 alive cancer free | 2005 | 13 |
| 15   | 56  | – – | – | 15 | 534 | Multiple | Peritoneum | Bilateral | Bilateral SO* | TAE, Cx* | – | 5 alive | 1999 | 14 |
| 16   | 40  | RFA | TACE | N/A | 2150 | N/A | Peritoneum | Bilateral | Bilateral SO (with TAH and sigmoidectomy) | N/A | N/A | 2006 | 15 (Korean) |
| 17   | 61  | Hepatectomy | RFA, PEIT | TACE, SBRT | 11 | 1862 | – | Peritoneum | Bilateral | Bilateral SO, peritoneal resection | 5-FU based regimens, SOR, ramucirumab | 132 alive | Present case |

RFA radiofrequency ablation, PEIT percutaneous ethanol injection therapy; TAC(E)E, transarterial (chemo)embolization, Cx chemotherapy, SOR sorafenib, SBRT stereotactic body radiation therapy, SO salpingo-oophorectomy, TAH total abdominal hysterectomy, 5-FU 5-fluorouracil, N/A not applicable

*Details not known

**The sizes of five ovaries with tumors in these three cases were 4, 5, 6.5, 10, and 11 cm. Individual sizes are not described
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