Clinical Journal of Gastroenterology (2019) 12:128–134
https://doi.org/10.1007/s12328-018-0918-5

CASE REPORT

Combined hepatocellular-cholangiocarcinoma successfully treated with sorafenib: case report and review of the literature

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Received: 28 August 2018 / Accepted: 20 October 2018 / Published online: 29 October 2018

Abstract

Sorafenib, a multiple kinase inhibitor, has been established as first-line standard systemic chemotherapy for patients with advanced hepatocellular carcinoma (HCC). We encountered a patient with combined hepatocellular and cholangiocarcinoma (CHC) who achieved complete remission in response to sorafenib treatment. A 58-year old man with hepatitis C virus (HCV)-induced liver cirrhosis was diagnosed with CHC in segments 6th and 7th of the liver and underwent partial surgical resection. Three months later, CHC recurred as metastases at multiple intrahepatic sites, lymph nodes, and bones, making surgery impossible. Treatment with sorafenib was initiated at 400 mg b.i.d., later reduced to 400 mg/day. After 6 months of sorafenib administration, he no longer showed abnormal uptake on fluorodeoxyglucose positron emission tomography. He was continued on sorafenib for 2.5 years, but later discontinued due to adverse events. He has shown no evidence of tumor recurrence more than 1 year after sorafenib discontinuation. His HCV was eradicated by direct-acting antivirals, and he remains in good health.

Keywords Combined hepatocellular-cholangiocarcinoma · Sorafenib · Cirrhosis · Hepatitis C virus · Systemic chemotherapy

Introduction

Combined hepatocellular cholangiocarcinoma (CHC) is a rare tumor, accounting for 0.8% of primary liver tumors [1]. CHC, which consists of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) [2, 3], frequently develops in livers chronically damaged by viral hepatitis or cirrhosis. Surgical resection is the first-line treatment if the tumor is resectable; however, prognosis is extremely poor, with a 2-year postoperative survival rate of 16% [4]. To date, effective chemotherapy has not been determined for CHC, and no randomized trials have yet been performed [5].

Sorafenib is a small molecule multi-kinase inhibitor that blocks rapidly accelerated fibrosarcoma (RAF) kinase, vascular endothelial growth factor-2/-3 (VEGF-2/-3), platelet-derived growth factor β (PDGFβ), Flt3 and c-kit receptor [6]. Sorafenib has been approved as first-line treatment for patients with unresectable intermediate and advanced HCC, suggesting that it may be effective in patients with unresectable CHC. This report describes a patient with multiple intrahepatic and extrahepatic metastases of CHC after resection who achieved complete remission after treatment with sorafenib, and even after cessation of treatment.

Case report

A 58-year old Japanese man was diagnosed with a liver tumor. His medical history included hypertension, for which he was being treated with azelnidipine and candesartan, and a cerebral hemorrhage in his 40 s, with no aftereffects. He had smoked 30 cigarettes per day for 10 years, but had quit smoking at the time of presentation, and drank one can of beer once a week. He had been diagnosed in his 40 s with hepatitis C virus (HCV) infection. Despite treatment with interferon and ribavirin, followed by peginterferon and ribavirin, HCV was not eradicated. He was heterozygous for an interleukin-28B single nucleotide polymorphism, making HCV eradication by interferon-based therapy difficult [7].

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At age 54 years, he underwent a Hassab operation and splenectomy to prevent bleeding of progressing esophagogastric varices. He was followed-up every 6 months by abdominal ultrasonography, and every year by gadolinium ethoxybenzyl diethylene triamine penta-acetic acid (Gd-EOB-DTPA)-enhanced hepatic MRI (EOB-MRI).

Follow-up EOB-MRI at age 58 years showed a single 35 mm tumor in segment 6/7th of his right hepatic lobe. The tumor appeared as a low-intensity area on plane phase (Fig. 1a), marginal enhancement on arterial phase (Fig. 1b), edge dyeing on portal phase (Fig. 1c), and mild internal uptake on hepato-biliary phase with no uptake in the central zone (Fig. 1d), suggesting necrosis. This EOB-MRI image pattern was atypical for classical hepatocellular carcinoma (HCC) and implied to be a combined hepatocellular cholangiocarcinoma (CHC) or poorly differentiated HCC. Dynamic contrast computed tomography showed the tumor had the same vascular pattern. Blood concentrations of tumor markers showed that α-fetoprotein (AFP) was 21.4 ng/mL, AFP-L3 was 10.6%, des-γ-carboxy prothrombin (DCP) was 48 AU/L, carcinoembryonic antigen (CEA) was 2.0 ng/mL, carbohydrate antigen 19−9 (CA19-9) was 85 U/mL, detection of pancreatic cancer-associated antigen (DUPAN2) was 776 U/mL, and s-pancreas-1 antigen (SPan-1) was 108.6 U/mL (Fig. 2). Thus tumor markers for HCC such as AFP and DCP were elevated, as were those for CC such as CA19-9, DUPAN2 and SPan-1. These patterns, along with radiologic findings, suggested a diagnosis of CHC. Although his liver function was almost preserved (Serum albumin (Alb) 3.3 g/dL, prothrombin time (PT) activity 72%, total-bilirubin (T-Bil) 0.9 mg/dL, with no ascites and no encephalopathy, Child-Pugh score 6 points), 15-min retention ratio of indocyanin green test was 31%. Laparoscopic partial hepatectomy was then performed, and the tumor was completely resected. Pathological examination showed two components, involving adenocarcinoma and HCC. Hematoxylin-eosin staining showed that the tumor consisted primarily of the adenocarcinoma component (Fig. 3a), accompanied by the eosinophilic trabecular structure of the HCC component (Fig. 3b). Immunohistochemical staining showed that both the adenocarcinoma and HCC regions were positive for cytokeratin 8/18 (CK8/18) (Fig. 3c, e) and CK7 (Fig. 3d, f). Some carcinoma cells were also positive for neural cell adhesion molecule (NCAM)

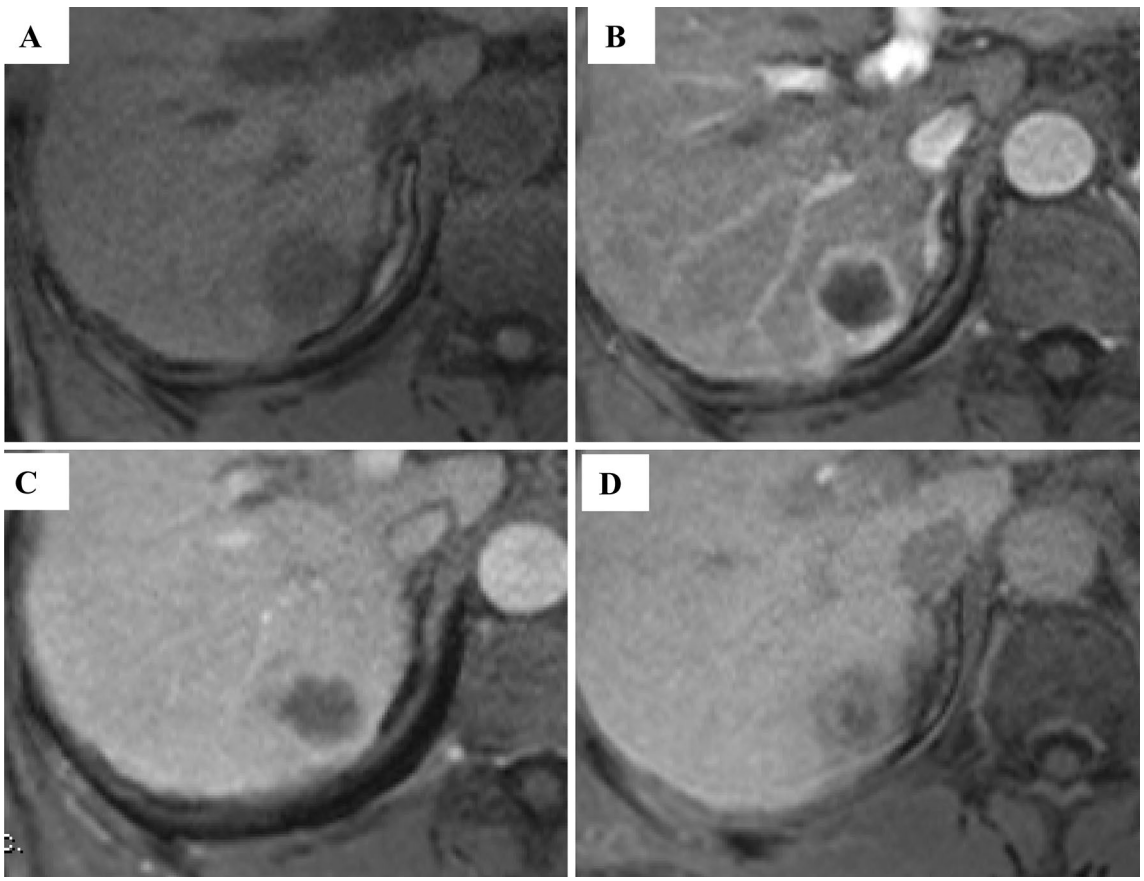

Fig. 1 Gd-EOB-DTPA-enhanced hepatic MRI at initial diagnosis, showing a liver tumor in segment 6/7 th. **a** Low density area in plane phase. **b** Marginal enhancement in arterial phase. **c** Internal low intensity in portal phase. **d** Central heterogeneous uptake in hepato-biliary phase

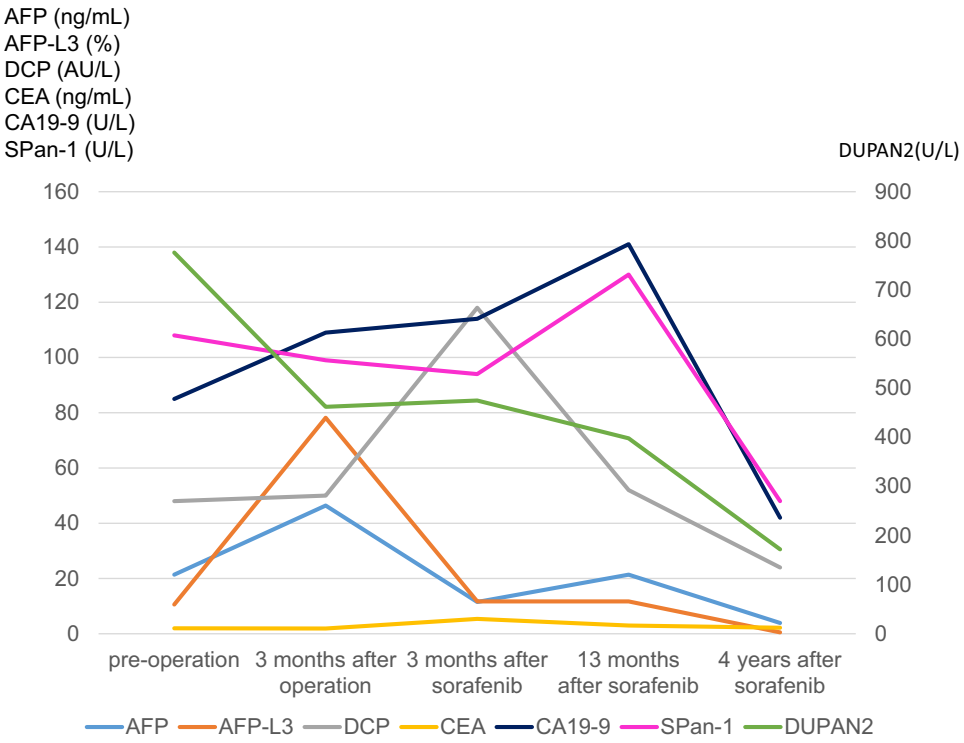

Fig. 2 Changes of tumor markers in present case. Left Y-axis represents the titer of AFP (ng/mL), AFP-L3 (%), DCP (AU/L), CEA (ng/mL), CA19-9 (U/L) and SPan-1 (U/L). Right Y-axis represents the titer of DUPAN2 (U/L). X-axis represents the indicated time. Each color line in the graph represents indicated tumor marker. *SVR* sustained viral response, *AFP* alpha fetoprotein, *DCP* des-gamma-carboxy prothrombin, *CEA* carcinoembryonic antigen, *CA19-9* carboyhydrate antigen 19-9; DUPAN2, detection of pancreatic cancer-associated antigen, *SPan-1* s-pancreas-1 antigen

(Fig. 3g). Noncancerous regions of the liver were cirrhotic, accompanied by marked pseudocholangiolar proliferation. The patient was diagnosed pathologically as having CHC with stem cell features intermediate cell subtype, as classified by the World Health Organization (WHO) in 2010 [3].

Three months after the operation, EOB-MRI showed multiple intrahepatic CHC recurrences, with many small nodules present in the lateral segment of the liver. These nodules showed enhancement in arterial phase (Fig. 4a) and slightly low intensity in hepato-biliary phase, as well as low-intensity in T1 and high-intensity in T2 and diffusion weighted imaging [8]. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed increased accumulation at multiple sites in the cranium, left humerus, bilateral scapula, bilateral ribs, thoracic vertebra, lumbar vertebra, and right pubic area (SUV = ~ 11.56) (Fig. 4b). Furthermore, tumor markers for both HCC and CC were elevated (AFP, 46.4 ng/mL; AFP-L3, 78.2%; DCP, 50 AU/L; CEA, 1.9 ng/mL; CA19-9, 109 U/mL; DUPAN2, 462 U/mL; SPan-1, 99.5 U/mL) (Fig. 2), with AFP and AFP-L3 being higher than before the operation. Symptoms indicative of infection, such as fever, were not observed, and blood tests also did not suggest infection. The patient was, therefore, diagnosed with recurrence of CHC. His Child-Pugh score was seven points (Serum Alb 2.8 g/dL, PT-activity 64%, T-Bil 1.3 mg/dL, with no ascites and no encephalopathy).

Systemic chemotherapy was considered because of the rapidly growing intrahepatic and extrahepatic metastases. However, no standard chemotherapy regimen has yet been established for CHC. His liver function was decreased, however, his performance status was good. His serum creatinine concentration was 1.0 mg/dL, and his estimated glomerular filtration rate (eGFR) was 60.2 ml/min/1.73 m^2, suggesting a slight reduction in renal function. The standard chemotherapy regimen for CC consists of gemcitabine and cisplatin (GC), but this treatment was contraindicated by his decreased renal function. AFP and AFP-L3 concentrations were significantly higher than at initial diagnosis, suggesting that the HCC component may be preferentially involved in the development of metastases lesions.

He was started on sorafenib 400 mg bid. After 1 week, however, his platelet count decreased from $10.4 \times 10^4/\mu L$ to $6.0 \times 10^4/\mu L$. Therefore, his sorafenib dose was reduced to 400 mg/day. His general condition and hepatic reserve function was almost preserved during sorafenib treatment although mild decrease of serum Alb and mild ascites were occasionally found. His blood pressure was kept to normal range with continuation of anti-hypertensive drugs. After 6 months of treatment, his platelet had gradually recovered to baseline ($11.6 \times 10^4/\mu L$). FDG-PET after two months of sorafenib treatment showed a reduction in accumulation by multiple bone and lymph node metastases (SUV = ~ 8.79) (Fig. 4c), while FDG-PET after 6 months of sorafenib administration showed complete disappearance of FDG accumulation (Fig. 4d). EOB-MRI showed no early enhancement of liver metastasis in arterial phase (Fig. 4f). Blood tests showed that AFP was 11.5 ng/ml, AFP-L3 was 11.7%, DCP was 118 AU/L, CEA was 5.4 ng/

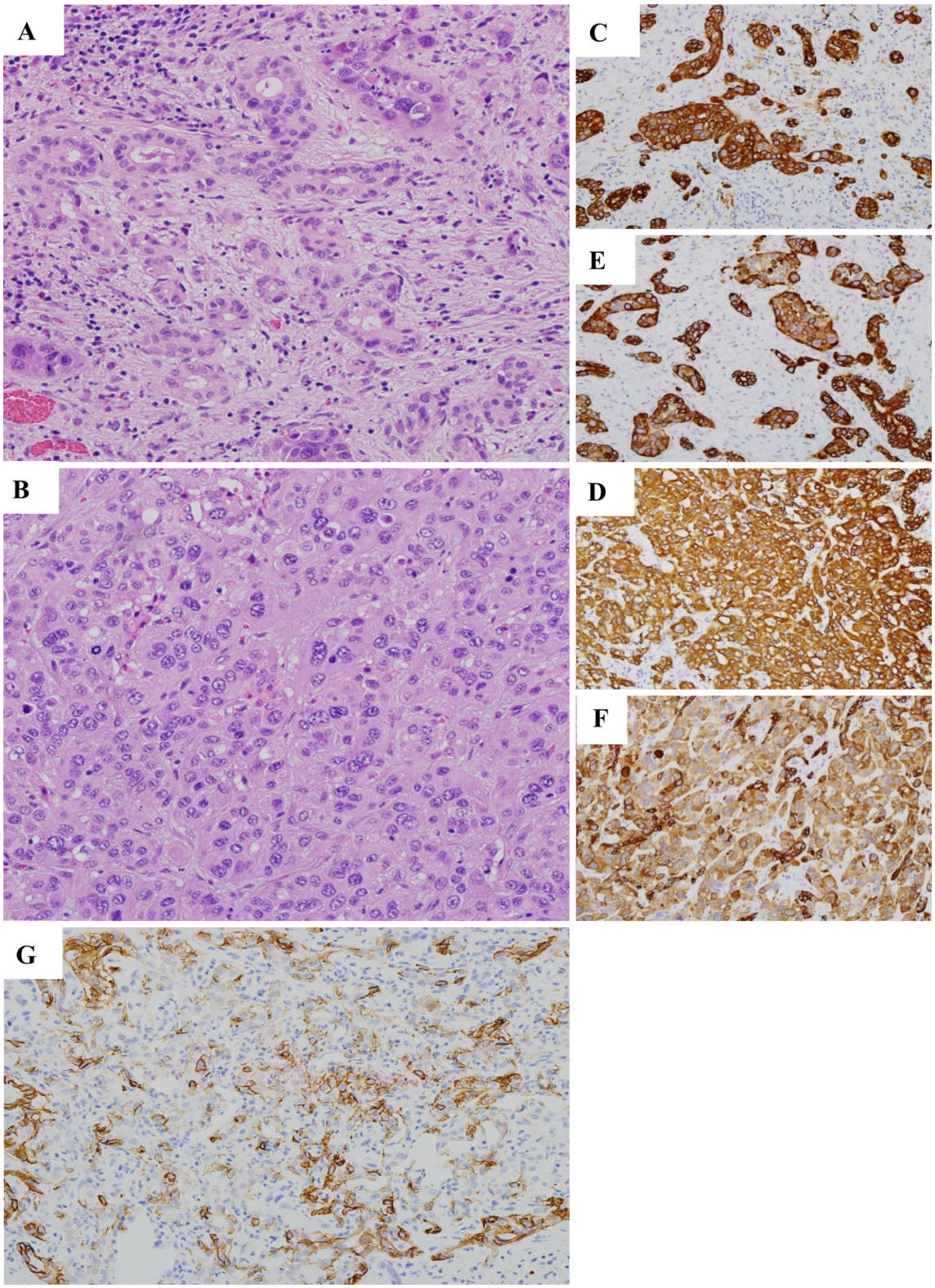

Fig. 3 Photograph of the tumor specimen, showing combined hepatocellular-cholangiocarcinoma with stem cell features. **a** Hematoxylin-eosin staining, adenocarcinoma component. **b** Hematoxylin-eosin staining, HCC component. **c** Immunostaining for CK8/18, adenocarcinoma component. **d** Immunostaining for CK7, adenocarcinoma component. **e** Immunostaining for CK8/18, HCC component. **f** Immunostaining for CK7, HCC component. **g** Immunostaining for NCAM. Original magnification x200

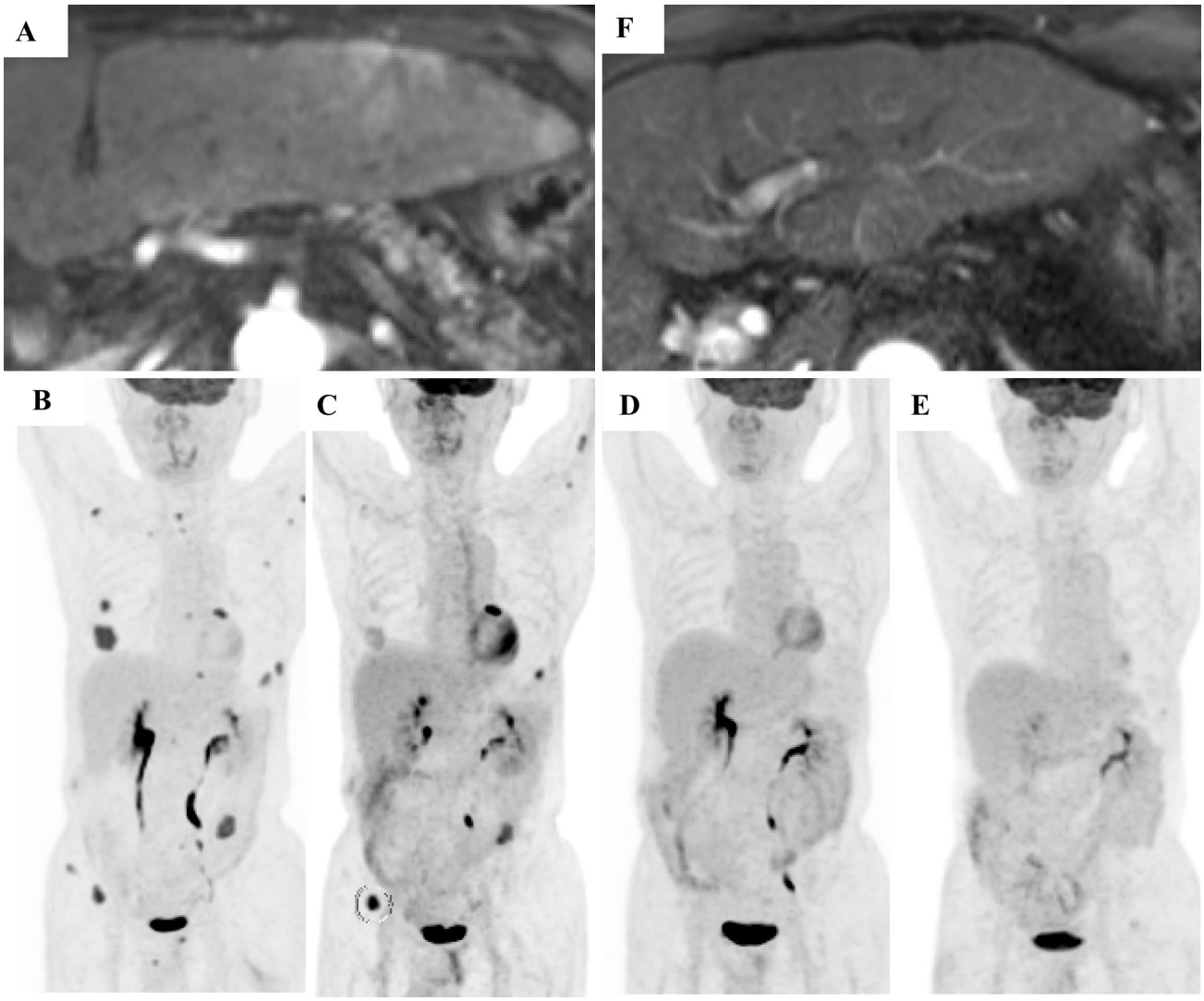

Fig. 4 EOB-MRI **a, f** and FDG-PET **b–e** images. **a** Slight early enhancement in the lateral segment of the liver in arterial phase. **b** FDG-PET at recurrence, showing multiple areas of abnormal uptake. **c** FDG-PET after 3 months of sorafenib treatment, showing abnormal uptake was unclear. **d** FDG-PET after 6 months of sorafenib treatment, showing complete disappearance of abnormal uptake. **e** FDG-PET after 1 years of sorafenib cessation, showing no recurrence of the tumor. **f** EOB-MRI after 6 months of sorafenib treatment, showing complete disappearance of early enhancement during arterial phase

mL, CA19-9 was 114 U/mL, DUPAN2 was 475 U/mL, and SPan-1 was 94 U/mL (Fig. 2), indicating marked reductions in AFP and AFP-L3 concentrations. Side effects occurring at the same time included diarrhea and melena. Esophagogastroduodenoscopy, capsule endoscopy and total colonoscopy showed non-specific erosions of the intestinal mucosa, suggesting adverse events of long-term sorafenib treatment. His sorafenib dose was further decreased, to 400 mg every other day for 18 months. He continued to experience occasional symptoms related to gastrointestinal mucosal injury. Thirty months after starting sorafenib, he was discontinued. After discontinuation of sorafenib, diarrhea and melena completely disappeared. FDG-PET showed no recurrence 1 year after sorafenib discontinuation (Fig. 4e). He was subsequently treated with sofosbuvir and ledipasvir for HCV infection, and he achieved a sustained viral response (SVR). AFP, AFP-L3, CA19-9, DUPAN2 and SPan-1 further decreased to within normal ranges (Fig. 2). Four years after the initial diagnosis of CHC, the patient is healthy, with no recurrence of CHC.

Discussion

Prognosis is generally poor in patients with CHC, and standard systemic chemotherapy regimens have not yet been established [5]. We encountered a patient with advanced CHC who was successfully treated with sorafenib. Sorafenib

had a curative effect, with complete remission maintained after treatment discontinuation.

At clinical diagnosis of CHC recurrence, the patient presented with multiple metastatic lesions involving bones, lymph nodes and multiple intrahepatic nodules. Moreover, tumor markers of HCC were elevated, suggesting that these metastases preferentially involved the HCC component. We, therefore, administered sorafenib, a standard systemic treatment for advanced HCC [9]. Previous studies (Table 1) have reported that sorafenib treatment may prolong survival in patients with CHC [10, 11] and CC [12]. Phase 2 trials and cohort studies in patients with CC found that sorafenib was associated with survival benefits, such as longer tumor control or survival, in a limited number of patients, although the overall treatment results were unsatisfactory [13–16]. Clinical trials showed maximum overall survival of 36 and 33 months in some patients [13, 15]. In contrast, a recent study found that the efficacy of sorafenib for the treatment of CHC was poor, suggesting that platinum-containing regimens such as GC may be more effective; this study, however, included very few patients treated with sorafenib [17]. Advanced CHC cases preferentially involving CC component might be considered to treat firstly with GC regimen. The effects of sorafenib in CHC remain unclear, suggesting the need for additional investigations.

The mechanisms underlying the effectiveness of sorafenib in our patient remain unclear. The metastatic sites may have involved the HCC rather than the CC component, as shown by the effects of sorafenib treatment on tumor markers, and the findings of EOB-MRI such as early enhancement in arterial phase. Alternatively, sorafenib may be as effective against the CC component or the CHC itself. Sorafenib has been shown to inhibit cell-proliferation signals and induce apoptosis of CC cells [18], as well as inhibiting the proliferation of CC cells with cancer-stem cell such as features [19]. The levels of expression of *FLT3, TP53, FGFR4*, and *EGFR* were higher on CHC than HCC or CC cells [20], differences that may have contributed to the favorable tumor control in the present patient. Furthermore, CHC subtypes with stem-cell features showed clinicopathological differences [21], suggesting that precise treatment may require detailed examinations of phenotype or gene expression. Finally, our patient was treated with sorafenib for 30 months, in agreement with a previous case report showing that long-term sorafenib therapy achieved complete remission in a patient with advanced HCC [22]. Long-term sorafenib treatment may induce favorable responses, such as vascular normalization of the tumor.

This study had several limitations. The nature of the recurrent lesions could not be confirmed histologically, nor could the mechanism by which sorafenib acts on these lesions. Although alterations in tumor marker concentrations suggested that the HCC component was preferentially involved, this could not be determined definitively. Furthermore, genetic examinations could not be performed on this patient. Interestingly, the concentrations of CC-associated tumor markers also decreased after SVR to HCV treatment, although treatments for cancer were not administered at the same time. The association between HCV and these tumor markers are unclear, although HCV may contribute to CHC carcinogenesis or stem cells. Further investigations are warranted. Furthermore, the indication of sorafenib should be considered carefully. In present case, decreased liver function and past-history of hypertension and cerebral hemorrhage were found. Careful monitoring of adverse events and intervention for blood pressure were required. We should consider carefully to administer sorafenib for CHC case by case.

In conclusion, we encountered a patient with advanced CHC who achieved complete remission after long-term sorafenib treatment and maintained remission after sorafenib discontinuation. Sorafenib might be a useful treatment

Table 1 Results of sorafenib treatment for biliary cancer or combined hepatocellular cholangiocarcinoma

Diagnosis	Number of patients	Study design	Treatment	PFS [95% CI]* (months)	OS [95% CI]* (months)	Ref
CHC	1	Case report	Sora→DOX + CDDP→5FU	n/e	18	[9]
CHC	3	Case report	Sora	2.7–6.9	3.3–17.5	[10]
CHC	5	Retrospective sora	1.6 [1.2-2.0]	3.5 [0.0–7.6]	[16]	
Biliary ca	31	Phase 2	Sora	3 [2–4]	9 [4–12]	[12]
Biliary ca	46	Phase 2	Sora	2.3 [0–12]	4.4 [0–22]	[13]
Biliary ca	15	Retrospective	Sora	5.5 [3.9–7.1]	5.7 [5.0–6.4]	[14]
CCC	44	Pilot	Sora	3.2 [2.4–4.1]	5.7 [3.7–8.5]	[15]
CCC	1	Case report	Sora	n/e	48	[11]

PFS progression-free survival, *OS* overall survival, *CI* confidence interval, *Ref* reference, *CHC* combined hepatocellular cholangiocarcinoma, *Sora* sorafenib, *DOX* doxorubicin CDDP, cisplatin, *5FU* 5-fluorouracil, *ca*. cancer, *CCC* cholangiocellular carcinoma, *n/e* not evaluated

*If available

option for patients with advanced CHC. Further investigations regarding phenotype and gene expression in individual patients with CHC case are required for precision medicine.

Compliance with ethical standards

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

Human/animal Rights All procedures followed have been performed in accordance with the ethical standards laid downin the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Informed consent was obtained from a patient for being included in the study.

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