Am J Transl Res 2025;17(5):3538-3545
www.ajtr.org /ISSN:1943-8141/AJTR0161579

Case Report

Case report of complete remission in two patients with Barcelona stage C hepatocellular carcinoma treated with apatinib combined with camrelizumab

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Received October 30, 2024; Accepted April 24, 2025; Epub May 15, 2025; Published May 30, 2025

Abstract: Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide. Due to its insidious onset and nonspecific clinical manifestations, most patients are diagnosed at an advanced stage and are no longer candidates for curative surgical resection. Treatment options for advanced HCC remain limited. Immunotherapy, particularly immune checkpoint inhibitors, in combination with anti-angiogenic agents, has emerged as a promising therapeutic strategy. Several studies have demonstrated the safety and efficacy of apatinib combined with camrelizumab in various solid tumors; however, complete remission is rarely reported. This report presents two cases of Barcelona Clinic Liver Cancer (BCLC) stage C HCC that achieved complete remission following treatment with apatinib plus camrelizumab. According to the Response Evaluation Criteria in Solid Tumors, both patients achieved complete response, allowing for drug discontinuation.

Keywords: Apatinib, camrelizumab, liver malignancy, cure

Introduction

Primary liver cancer is the most common malignancy of the digestive system worldwide, with hepatocellular carcinoma (HCC) accounting for over 90% of cases [1, 2]. In Asia, liver cancer is often associated with chronic liver disease, primarily due to chronic hepatitis B virus (HBV) infection [3-5], which gradually progresses to cirrhosis. Approximately 80% of liver cancers develop on the basis of cirrhosis. Cirrhosis-related complications, such as gastrointestinal bleeding, ascites, and hepatic encephalopathy, significantly increase patient morbidity and mortality. The cumulative 5-year risk of developing liver cancer in patients with cirrhosis ranges from 5% to 30% [6].

Due to its insidious onset and nonspecific clinical manifestations, liver cancer is often diagnosed at an advanced or metastatic stage. As a result, effective treatment strategies for unresectable or advanced HCC are urgently needed. Immune evasion plays a crucial role in HCC pathogenesis, where activation of immune checkpoints suppresses antitumor immunity and facilitates tumor progression. Immune checkpoint inhibitors (ICIs) can counteract this mechanism and inhibit tumor growth [7].

Camrelizumab is a novel humanized IgG4 monoclonal antibody targeting programmed death-1 (PD-1), which blocks its interaction with programmed death-ligand 1 (PD-L1), thereby restoring T-cell function and exerting antitumor effects. Based on a prospective, randomized, multicenter phase II clinical trial in China evaluating camrelizumab in advanced HCC patients who had failed prior systemic therapies, the China Food and Drug Administration approved camrelizumab on March 4, 2020, for patients previously treated with sorafenib and/or oxaliplatin-based chemotherapy. It became the first PD-1 inhibitor approved in China for liver cancer, marking a significant milestone for domestic ICIs in this field [8].

https://doi.org/10.62347/HWOV2961

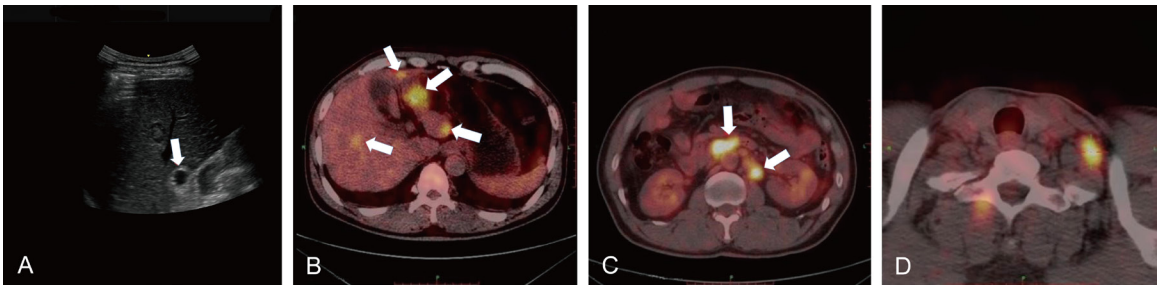

Figure 1. Abdominal ultrasound images. A. Multiple hypoechoic nodules of varying sizes in the liver. B. Multiple slightly low-density nodules and space-occupying lesions in the liver. C. Multiple retroperitoneal lymph nodes. D. Multiple enlarged lymph nodes in the left supraclavicular region, not excluding lymph node metastasis.

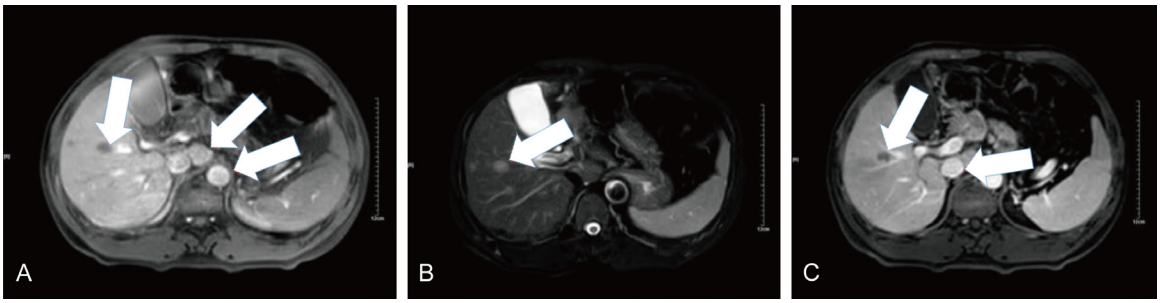

Figure 2. Hepatobiliary and pancreatic plain scan + enhanced CT. A. Enhanced scan during the arterial phase shows marginal ring-like enhancement, with multiple enlarged lymph nodes in the retroperitoneal and portal venous spaces. B. On the fat-suppressed sequence, scattered roundish slightly hyperintense nodules are seen in the liver parenchyma. C. During the portal venous phase, the degree of enhancement is reduced, with multiple enlarged lymph nodes in the retroperitoneal and portocaval spaces. CT: computed tomography.

Tumor angiogenesis, a critical step in tumor growth and metastasis, supplies oxygen, nutrients, and growth factors to cancer cells. Apatinib, a first-generation oral anti-angiogenic agent, selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR-2) and has demonstrated antitumor activity in various cancers [9, 10].

Here, we report two cases of advanced HCC treated with camrelizumab combined with apatinib at our hospital. Both patients achieved complete remission, with complete disappearance of tumor lesions. These cases suggest a potential synergistic effect of combining immunotherapy with anti-angiogenic therapy in the treatment of advanced HCC.

Case report

Case 1

A 56-year-old male presented to a local hospital on December 19, 2020, with a chief complaint of abdominal pain lasting one week. Abdominal computed tomography (CT) revealed small patchy low-density areas in the left hepatic lobe, suggestive of possible neoplastic lesions or cholangiocarcinoma. His serum alpha-fetoprotein (AFP) level was markedly elevated at 531.99 ng/mL (reference range: 0-7 ng/mL). Based on these findings, the patient was referred to our hospital for further evaluation and management.

The patient had a 20-year history of chronic HBV infection without prior antiviral treatment. He reported occasional alcohol consumption and had no family history of HBV or liver cancer. Physical examination showed mild tenderness in the right abdomen; other findings were unremarkable. The Eastern Cooperative Oncology Group performance status was grade 1. Laboratory tests revealed an AFP level of 615.23 ng/mL, normal bilirubin levels, and preserved liver function classified as Child-Pugh class A.

At our hospital, abdominal ultrasound showed multiple hypoechoic liver nodules of varying

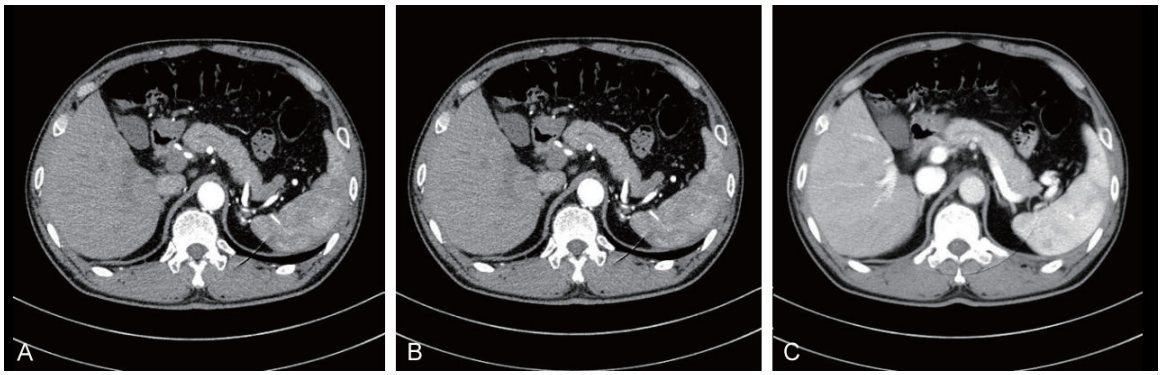

Figure 3. CT images of HCC at stage C. A, B. Enhanced CT during the arterial phase shows no definite abnormal enhancement foci within the liver. C. During the portal venous phase, a small nodular slightly hypoenhancing area is seen in the right lobe of the liver, indicative of HCC. CT: computed tomography; HCC: hepatocellular carcinoma.

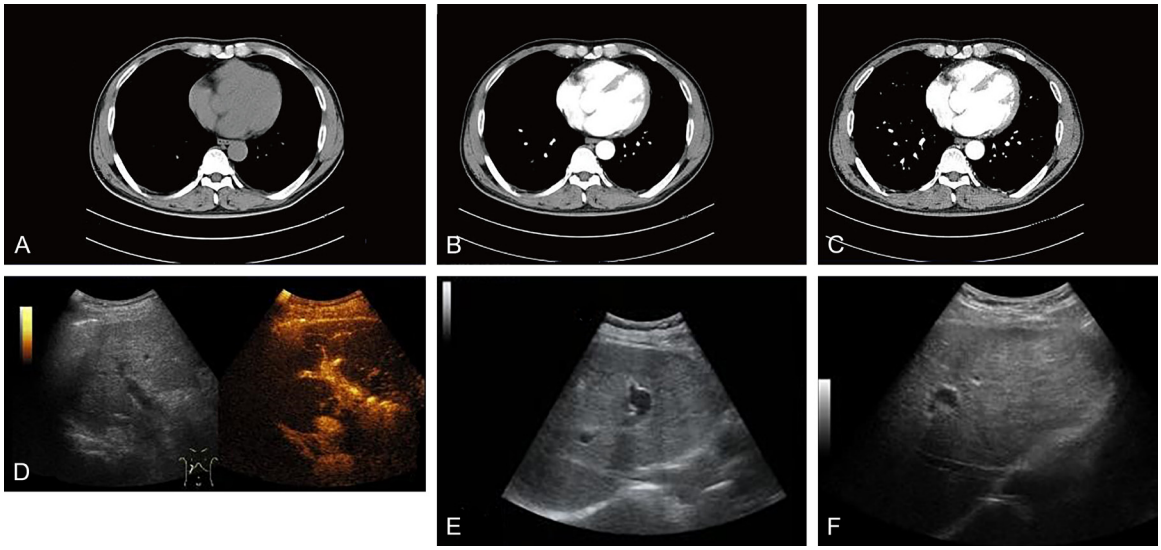

Figure 4. Ultrasound and CTA on May 28, 2022. A-C. CTA showed that the left lobe of the liver was reduced in size, and abnormal enhancing lesions in the right posterior lobe of the liver were not shown this time, confirming that the tumor lesion disappeared. D-F. Complete disappearance of the lesion on liver contrast-enhanced ultrasound. CTA: Computed Tomography Angiography.

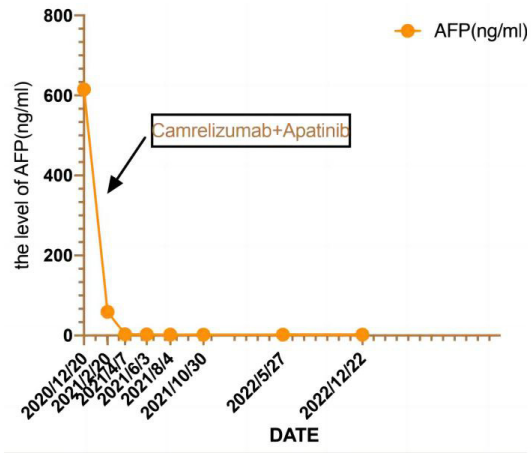

Figure 5. Clinical efficacy was evaluated by AFP levels and response to treatment. Molecular targeted therapy with oral apatinib (125 mg) once daily and camrelizumab intravenously every three weeks for more than 30 minutes each time. AFP, Alpha fetoprotein; Carrelizumab, Camrelizumab, Apatinib, Aitan-Apatinib mesylate. AFP: Alpha fetoprotein.

sizes, with the largest located in the right posterior lobe, measuring approximately 1.4 × 1.3 cm (**Figure 1A**). Positron emission tomography-computed tomography (PET-CT) revealed multiple slightly hypodense hepatic nodules and space-occupying lesions, the largest measuring 3.21 × 2.80 cm in the left lateral lobe

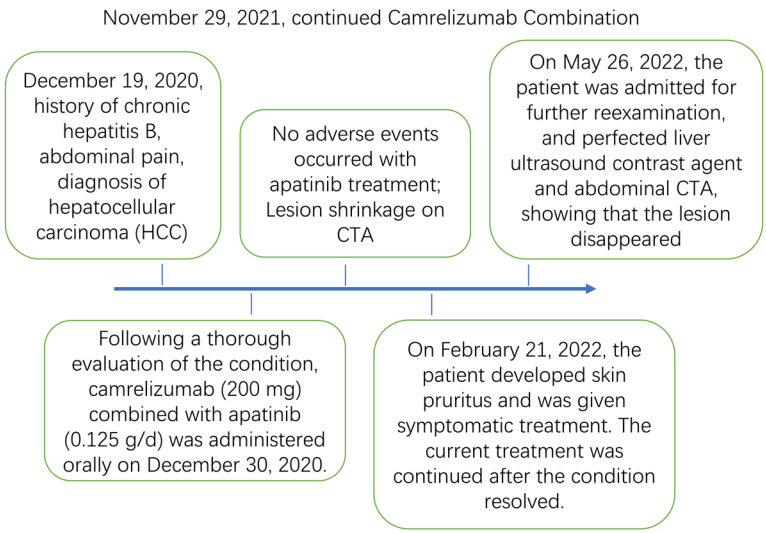

Figure 6. Clinical treatment course of Case 1. HCC: Hepatocellular carcinoma; CTA: Computed Tomography Angiography.

(**Figure 1B**). Additionally, PET-CT showed multiple retroperitoneal lymph nodes suspected of metastasis (**Figure 1C**) and hypermetabolic left supraclavicular lymph nodes on fluorodeoxyglucose (FDG) uptake, suggestive of lymph node metastasis (**Figure 1D**).

Further evaluation included contrast-enhanced CT of the hepatobiliary, pancreatic, and splenic regions (**Figure 2**) and liver biopsy, which confirmed hepatocellular carcinoma (HCC), staged as BCLC stage C (2022 criteria) (**Figure 3**).

Based on a comprehensive assessment, the patient was started on a combination of camrelizumab (200 mg, intravenously every 21 days) and apatinib (125 mg orally, once daily) from December 30, 2020. Follow-up on November 29, 2021, showed significant reduction in lesion size, with no reported adverse drug reactions. On February 21, 2022, the patient developed pruritus, which was managed symptomatically without discontinuing treatment.

By May 26, 2022, contrast-enhanced ultrasound and abdominal computed tomography angiography (CTA) showed complete resolution of the liver lesions (**Figure 4**). Superficial lymph node ultrasound showed no abnormalities in the cervical, clavicular, axillary, or inguinal regions. AFP levels had decreased to 2.07 ng/mL (**Figure 5**). Based on the Response Evaluation Criteria in Solid Tumors (RECIST), the patient was assessed as having achieved complete remission. The disease course and treatment timeline are illustrated in **Figure 6**.

Case 2

A 50-year-old male presented to our hospital in October 2019 with a 19-year history of hepatitis B and recent unintentional weight loss over the preceding three months. He had been diagnosed with hepatitis B surface antigen positivity during a routine checkup 19 years earlier and had been receiving antiviral therapy with tenofovir disoproxil fumarate (Viread) regularly. Three months prior to admission, he experienced a weight loss of 8 kg and sought evaluation at a local hospital, where HCC with multiple intrahepatic metastases was suspected.

The patient had a history of hypertension, controlled with medication, and denied smoking or alcohol use. Physical examination was unremarkable, and his Eastern Cooperative Oncology Group performance status was grade 1. Laboratory tests revealed an AFP level of 560.91 ng/mL, normal bilirubin levels, and preserved liver function classified as Child-Pugh class A.

Initial abdominal ultrasound on admission showed no thoracic or abdominal effusion, diffuse hepatic parenchymal changes, multiple heterogeneous medium-echo space-occupying lesions (classified as Liver Imaging Reporting and Data System [LI-RADS] LR-4), splenomegaly, and dilation of the splenic vein, suggestive of malignancy. Subsequent PET-CT (**Figure 7**) revealed an irregular high-density mass in the right hepatic lobe measuring approximately 9.35 × 7.48 cm, consistent with a hepatic malignancy. Multiple hyperdense intrahepatic nodules, lung nodules, and FDG-avid retroperitoneal lymph nodes were also detected, indicating probable metastases. Abdominal CTA images are shown in **Figure 8**.

Due to the presence of adjacent large blood vessels and the high risk of hemorrhage, liver biopsy could not be performed under ultra-

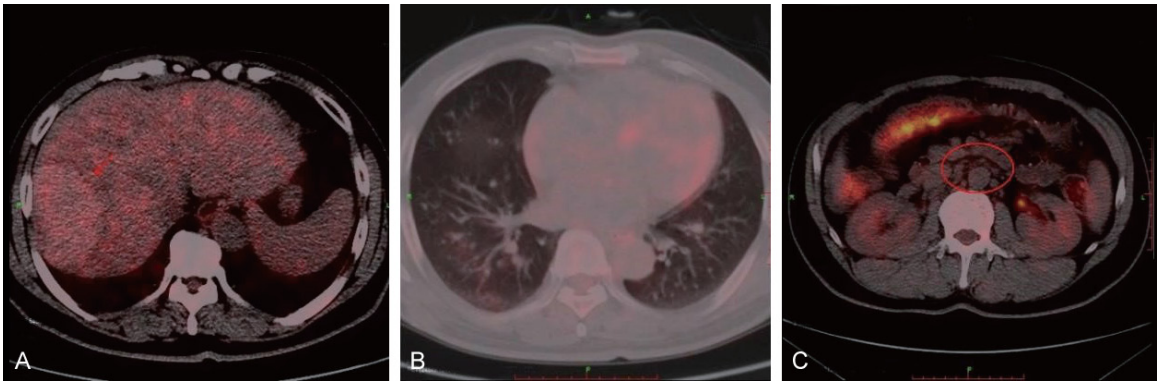

Figure 7. PET-CT images. A. A large irregular mass in the right lobe of the liver (9.35 × 7.48 cm). B. Multiple nodules in bilateral lung, considering carcinomaous nodules and hyperplastic nodules. C. Multiple lymph nodes in the retroperitoneal region, not excluding metastasis. PET-CT: Positron emission tomography/computed tomography.

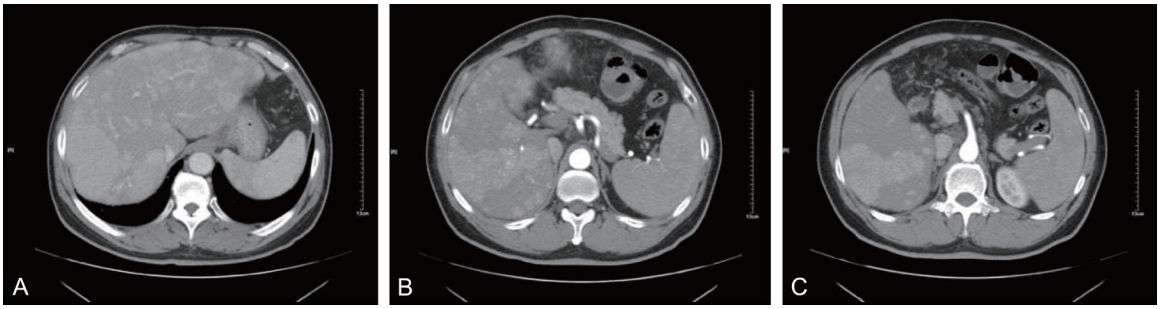

Figure 8. Abdominal CTA images. A-C. Enhanced scan during the arterial and portal venous phases shows multiple nodular and mass-like abnormal enhancement foci of varying sizes within the liver parenchyma. The larger lesion in the right lobe of the liver is highly suggestive of a malignant lesion. CTA: Computed Tomography Angiography.

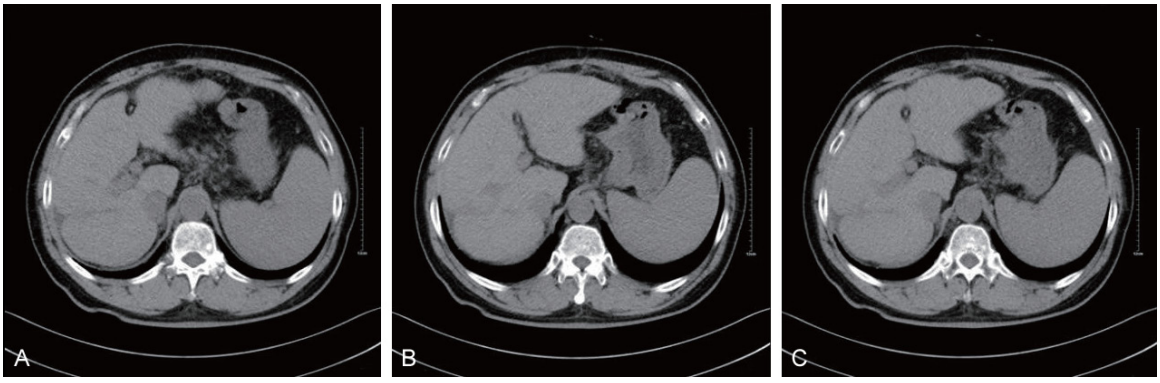

Figure 9. Abdominal CTA on April 8, 2022. A-C. Localized indentation at the liver margin of the right hepatic lobe, with heterogeneous density in the adjacent liver parenchyma and patchy low-density areas. CTA: Computed Tomography Angiography.

sound guidance. As a result, histopathological confirmation and genetic testing could not be obtained at that time. Future genetic analysis may be required depending on disease progression.

On December 30, 2020, the patient began treatment with camrelizumab (200 mg intravenously every 21 days) combined with apatinib (250 mg orally once daily) and Tegafur, Gimeracil, and Oteracil Potassium Capsules

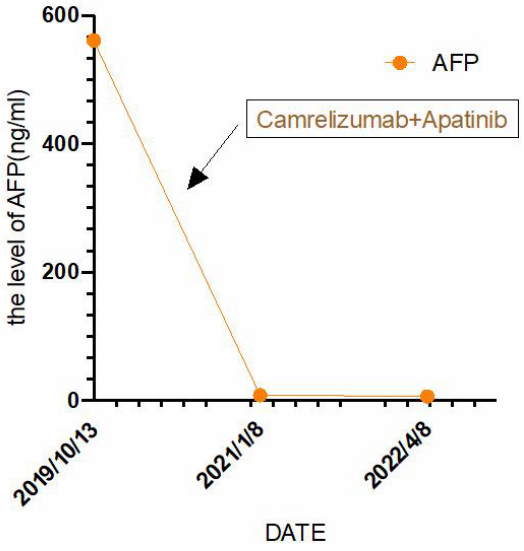

Figure 10. Clinical efficacy was evaluated by AFP levels and response to treatment. Molecular targeted therapy with oral apatinib (250 mg) once daily and camrelizumab intravenously every three weeks for more than 30 minutes each time. AFP, Alpha fetoprotein; Carrelizumab, Camrelizumab, Apatinib, Aitan-Apatinib mesylate. AFP: Alpha fetoprotein.

(50 mg twice daily). Antihypertensive therapy was continued without adjustment. Follow-up abdominal CTA on April 7, 2022 (**Figure 9**), showed focal depression of the liver margin in the right lobe, peripheral fluid attenuation, and scattered indistinct patchy and nodular lesions within the hepatic parenchyma on contrast enhancement. Lung CT revealed mild interstitial changes. Serum AFP levels decreased to 6.58 ng/mL (**Figure 10**). The clinical course and treatment are summarized in **Figure 11**.

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 revision of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case and accompanying images.

Discussion

In this report, we describe two patients with advanced BCLC stage C HCC who achieved complete remission following treatment with apatinib in combination with camrelizumab. The first patient experienced marked tumor regression and eventual complete disappearance of lesions, confirmed by a series of imaging studies. The second patient, diagnosed with multiple intrahepatic metastases, also demonstrated significant clinical improvement, with serum AFP levels returning to normal. These findings suggest that, even in cases with poor prognosis, a carefully selected combination of an anti-angiogenic agent and an immune checkpoint inhibitor can yield favorable therapeutic outcomes. This study highlights the potential of apatinib plus camrelizumab to deliver substantial clinical benefits in advanced HCC.

The VEGFR pathway can be effectively inhibited by several modalities, including neutralizing antibodies, tyrosine kinase inhibitors, and antisense or ribozyme-based approaches [11]. Apatinib is a selective VEGFR-2 inhibitor. In a prospective, randomized, double-blind, phase III clinical trial conducted in 2020 by Chinese researchers [12], apatinib demonstrated a significant improvement in overall survival in patients with advanced HCC when used as a second-line therapy (median OS: 8.7 months [95% CI: 7.5-9.8] vs. 6.8 months [95% CI: 5.7-9.1]; hazard ratio: 0.785 [95% CI: 0.617-0.998]; P = 0.048).

PD-1/PD-L1 inhibitors have shown promising clinical results across multiple tumor types [13]. Camrelizumab, developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd., is the first domestically produced PD-1 inhibitor in China. It demonstrated survival benefits in a single-arm phase II trial for relapsed/refractory classical Hodgkin lymphoma [14] and was approved by the China Food and Drug Administration on May 29, 2019. Currently, it is also used for non-small cell lung cancer, esophageal squamous cell carcinoma, gastric/gastroesophageal junction carcinoma, and HCC [15]. These data collectively support the role of VEGFR inhibitors and PD-1/PD-L1 antibodies in improving cancer treatment outcomes.

Several case studies and clinical trials have confirmed the efficacy and safety of apatinib and camrelizumab in oncology. For instance, a 56-year-old patient with non-small cell lung cancer harboring EGFR and KRAS mutations was treated with bevacizumab (400 mg), camrelizumab (200 mg), and pemetrexed (0.8 g), achieving disease control for over 17 months [16]. Another case involved a patient with gas-

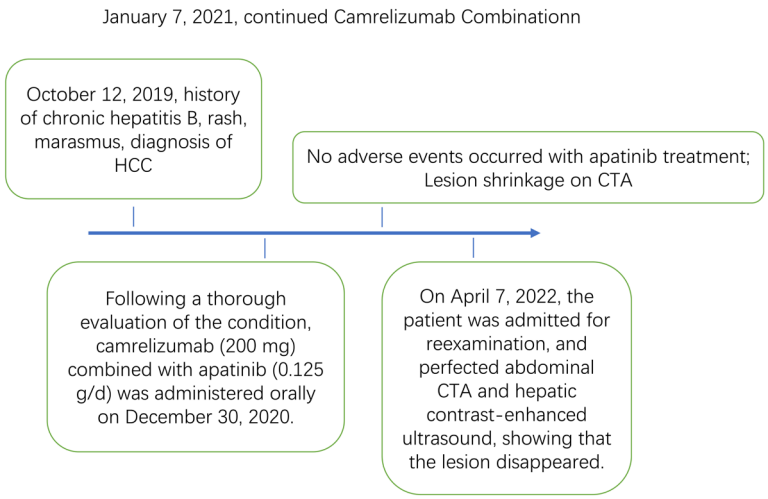

Figure 11. Clinical treatment course of case 2. HCC: Hepatocellular carcinoma; CTA: Computed Tomography Angiography.

tric cancer and liver metastasis treated at West China Hospital, Sichuan University [17]. After diagnostic confirmation through gastroscopic and liver biopsies, and molecular profiling of gastric, liver, and blood samples, lenvatinib (8 mg daily) plus camrelizumab (200 mg every two weeks) was initiated following transarterial chemoembolization. After 11 months, gastroscopy revealed complete disappearance of the gastric lesion, and no disease progression was observed at 14 months.

Inspired by results from an open-label, dose-escalation study on camrelizumab combined with apatinib in liver and gastric/esophagogastric junction cancers [18], we applied this combination therapy in our two patients. Remarkably, both achieved complete remission, with tumor disappearance and prolonged survival to date. Unfortunately, genomic testing was not performed in either case, which is a limitation. Given the heterogeneity and drug resistance of liver cancer, understanding the genetic underpinnings is crucial for precision medicine.

Relevant studies, such as the establishment of the LIMORE gene bank for liver cancer, have identified fibroblast growth factor 19 amplification and fibroblast growth factor receptor gene alterations as predictive biomarkers for lenvatinib responsiveness [19]. Additionally, international research teams have developed near-physiological in vitro liver organoid models for biomarker identification and drug screening. Using these platforms, extracellular signal-regulated kinase inhibitor SCH7-72984 has emerged as a potential therapeutic candidate for primary liver cancer [20]. These examples underscore the broad applicability and therapeutic promise of combination regimens involving apatinib and camrelizumab.

In conclusion, our case reports provide preliminary evidence supporting the efficacy of apatinib combined with camrelizumab as a treatment option for advanced HCC. While limited by the small sample size, the outcomes observed in these two cases suggest that this combination may offer significant clinical value. Given tumor heterogeneity, further large-scale studies are warranted to validate these findings. Moreover, incorporating molecular profiling may help identify patients most likely to benefit, facilitating personalized treatment strategies. Future research should focus on unraveling the molecular mechanisms underlying therapeutic responses to better guide clinical decision-making.

Disclosure of conflict of interest

None.

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