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Case Report
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Five-Year Complete Remission in Super-Giant Hepatocellular Carcinoma with Hepatectomy Followed by Sorafenib Plus Camrelizumab: A Case Report

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Abstract

Background: Cirrhotic patients with super-giant Hepatocellular Carcinoma (HCC), accompanied by portal vein invasion, generally face a poor prognosis. Although multitargeted Tyrosine Kinase Inhibitors (TKIs) and Immune Checkpoint Inhibitors (ICIs) present a promising treatment option, achieving long-term Complete Remission (CR) in a cirrhotic patient with super-giant HCC is rare.

Case Summary: A 40-year-old male with compensated hepatitis B-related cirrhosis was diagnosed with HCC, classified as BCLC stage C. Enhanced CT imaging revealed a 152 mm × 171 mm tumor in the right lobe of the liver, invading the right branches of the portal vein and hepatic vein. He had normal liver function tests, platelet count, International Normalized Ratio (INR), ICG-15, and liver stiffness measurements. The patient underwent a successful hepatectomy beyond current indications on July 2019. Unfortunately, HCC recurrence with lung metastases and a portal vein tumor thrombus was detected in December 2019. He promptly began treatment with TKI (Sorafenib, 200 mg twice daily) and ICI (Camrelizumab, a humanized anti-PD-1 monoclonal antibody, 200 mg every 3 weeks). On May 2020, the patient had achieved CR confirmed by enhanced CT and tumor markers. The dosage of Camrelizumab was adjusted to 200 mg every 12 weeks since June 2021 to March 2024. Despite effective control of the HCC, the patient experienced episodes of gastrointestinal bleeding, attributed to esophagogastric varices confirmed by gastroscopy, and treated with endoscopic variceal band ligation and cyanoacrylate injection. Remarkably, no further tumor recurrence and variceal bleeding were observed during 5-year follow-up every 6 months. Until now, the patient has survived for 5 years with complete and durable remission.

Conclusion: The combination of TKIs and ICs is a potentially effectiveness and feasibility for super-giant HCC patients with portal vein invasion after hepatectomy beyond current surgical indications. However, extensive using of TKIs plus ICIs raise two critical issues: (1) the need for effective endoscopic screening varices and management of portal hypertension in HCC patients, (2) the determination of optimal treatment duration as well as safe discontinuation of TKIs and ICIs in long-term CR HCC patients.

Keywords: Hepatectomy; Sorafenib; Camrelizumab; Super-giant hepatocellular carcinoma; Complete remission

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Introduction

Hepatocellular Carcinoma (HCC) is the most common type of primary liver cancer, originating from hepatocytes and intrahepatic cholangiocytes. It is the fourth most common malignancy and the second leading cause of cancer-related death in China, with Hepatitis B Virus (HBV) infection being a major causative factor [1]. According to the guidelines, patients with super-giant HCC, portal vein invasion, and extrahepatic spread are classified as advanced stage (BCLC stage C)

[2]. Despite the use of liver resection and Transcatheter Arterial Chemoembolization (TACE), the long-term prognosis for these patients remains extremely poor [3,4]. The advent of multitargeted Tyrosine Kinase Inhibitors (TKIs) and Immune Checkpoint Inhibitors (ICIs) has provided new hope for these patients. Sorafenib, a multi-targeted kinase inhibitor, has been extensively validated for the treatment of advanced HCC [5]. Camrelizumab are humanized monoclonal antibodies that target Programmed cell Death receptor 1 (PD-1), blocking its interaction with ligands PD-L1 and PD-L2 and restoring T-cell anti-tumor activity. Despite many studies has demonstrated the efficacy and safety of Sorafenib and Camrelizumab in patients with advanced HCC [6,7], long-term Complete Remission (CR) remains rare. Here, we present a case of a super-giant HCC with portal vein invasion. The patient underwent hepatectomy, followed by a combination therapy of Sorafenib and Camrelizumab, achieving a sustained CR over 5-year.

Case Presentation

In July 2019, a 40-year-old male was admitted to the hospital after an abdominal CT scan during a health examination revealed a hepatic space-occupying lesion. The patient had no significant medical history but had a family history of HBV infection. Physical examination showed tenderness in the right upper abdomen. Laboratory tests indicated positive HBsAg, elevated HBV DNA (5.28×10^3 IU/mL), elevated α-Fetoprotein (AFP) (575.9 ng/mL), and elevated AFP-L3 (206.8 ng/mL), with normal blood cell counts, liver and renal function, and coagulation tests (Table 1). Liver Stiffness Measurement (LSM) was 7.9 kPa, and the Indocyanine Green retention rate at 15 min (ICG R15) was 7.2%. Enhanced CT revealed a 152 mm × 171 mm liver mass in the right lobe with satellite nodules, invading the right posterior branch of the portal vein and the right hepatic vein. Thoracic CT showed no metastasis (Figure 1A).

Table 1: Laboratory examination at diagnosis and endpoint.

Variables		Baseline	End point
Peripheral blood test	WBC (× 10^9/L)	7.51	3.19
	RBC (× 10^9/L)	5.17	4.83
	HGB (g/L)	155	135
	PLT (× 10^9/L)	314	96
Coagulation test	PT (sec)	12.2	11.6
	INR	1.09	1.03
Biochemistry test	ALT (U/L)	25	28
	Tbil (μmol/L)	23.6	17.4
	ALP (U/L)	454	58
	γ-GT (U/L)	77	26
	ALB (g/L)	38.2	40.9
	CREA (μmol/L)	65	57
Tumor markers	AFP (ng/mL)	561.9	1.99
	AFP-L3 (ng/mL)	206.8	less than 0.908
Serology test	HBV-DNA (IU/mL)	5280	less than 10
	HBsAg+	Positive	Negative
	HBsAb	Negative	Negative
	HBeAg	Negative	Negative
	HBcAb	Positive	Positive
	HBeAb	Positive	Positive

WBC: White Blood Cell; RBC: Red Blood Cell; HGB: Hemoglobin; PLT: Platelet; PT: Prothrombin Time; INR: International Normalized Ratio; ALT: Alanine Transaminase; Tbil: Total Bilirubin; ALP: Alkaline Phosphatase; γ-GT: γ-Glutamyltransferase; ALB: Albumin; CREA: Creatinine; HBV: Hepatitis B Virus; AFP: α-Fetoprotein

The patient was diagnosed with HCC (BCLC stage C) and compensated hepatitis B-related cirrhosis (Child-Pugh class A, ECOG PS 0). He was prescribed entecavir for HBV infection and underwent hepatectomy beyond current surgical indications on July 18th, 2019 (Figure 1B, 2A). Pathological examination revealed moderately to poorly differentiated HCC with tumor thrombosis in most vessels, including the portal and right hepatic veins (Figure 2B). Immunohistochemical staining showed higher PD-1 expression in the tumor compared to surrounding tissue (Figure 2C-2E). On September 4th, 2019, the patient underwent TACE to reduce recurrence risk, confirming no tumor remnants.

Post-operation, the patient recovered well, with regular follow-up every 3 months, including serum AFP and enhanced CT scans, showing no recurrence until December 2019. At that time, he reported respiratory distress, and elevated serum AFP (134.7 ng/mL) and AFP-L3 (27.05 ng/mL). Enhanced CT scans identified multiple recurrent tumors in the liver and lungs (Figure 1C). The patient began treatment with Sorafenib (200 mg twice daily) and Camrelizumab (200 mg every 3 weeks) on December 2019. By February 2020, enhanced CT scans showed significant remission with tumor markers returning

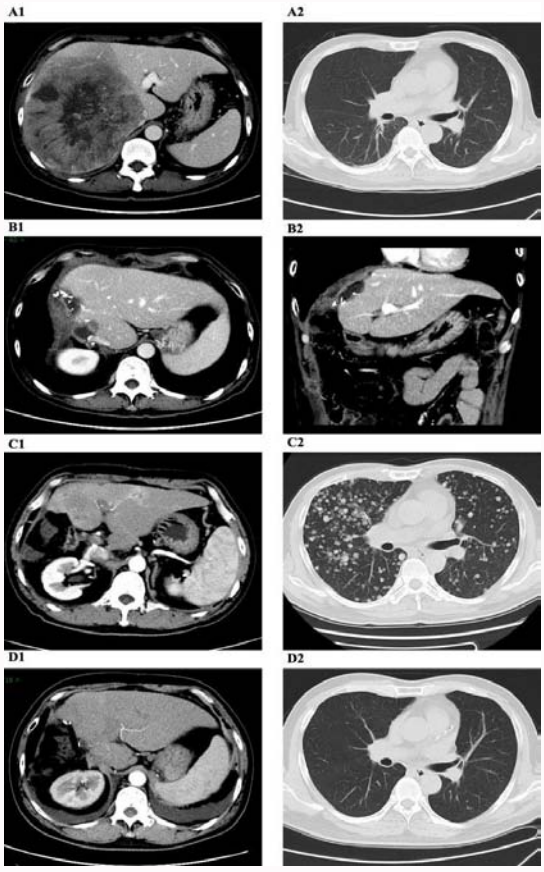

Figure 1: Contrast-enhanced abdominal CT and contrast-free thoracic CT. (A1, A2) CT scans showed a super-giant liver cancer with 152 mm × 171 mm in the right liver lobe, without lung metastasis. (B1, B2) The postoperative CT scans showed that HCC was removed. (C1, C2) CT scans showed multiple liver recurrences and lung metastasis on December 2019. (D1, D2) CT scans showed a complete remission of liver recurrence and lung metastasis on 12/5/2020.

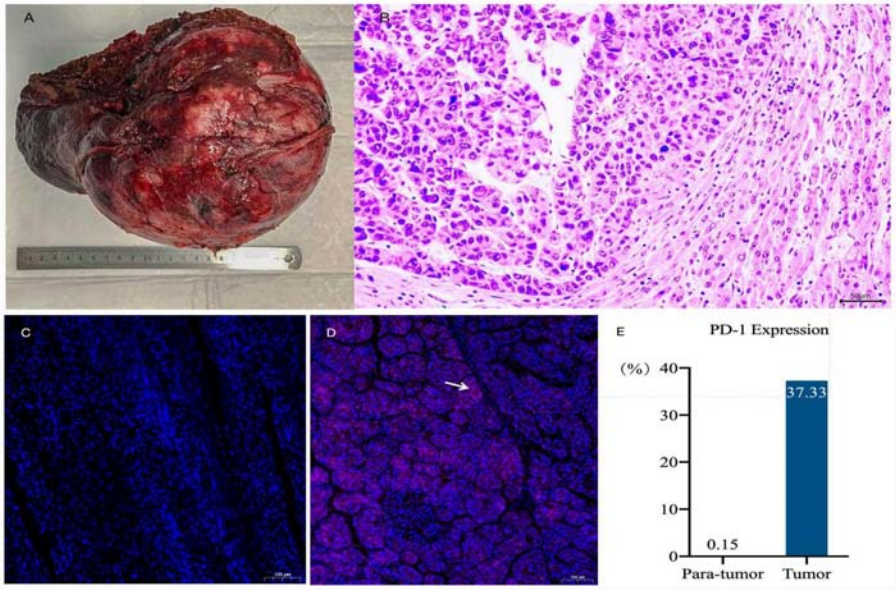

Figure 2: (A) The specimen showed a giant hepatic tumor over 170 cm in size. (B) Hematoxylin and eosin staining of HCC revealed that the tumor cell was arranged in a nest-like cluster at the junction with normal liver tissue, and the nuclear was large and deeply stained with atypical morphology. (200x magnification). (C-E) Immunofluorescence staining of PD-1 in tumor tissue was more positive than in para-carcinoma tissues. The arrow indicates positive.

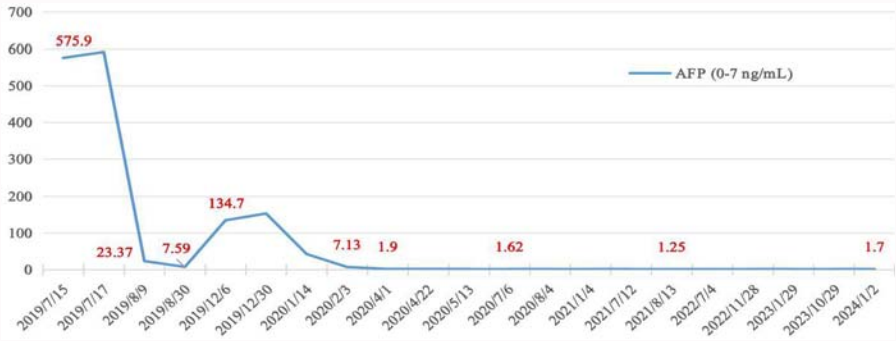

Figure 3: Dynamics change in AFP during the whole treatment.

to normal. The patient was diagnosed with CR on May 2020 (Figure 1D, 3). Since June 2021, the dosage of Camrelizumab was reduced to 200 mg every 12 weeks, with the final infusion administered on March 2024. During the follow-up, the patient experienced two episodes of gastrointestinal bleeding due to mild esophagogastric varices on May 12th, 2020 and July 11th, 2021 separately, treated with Endoscopic Variceal band Ligation (EVL) and cyanoacrylate injection on May 29th, 2020 and August 13th, 2021, respectively (Figure 4). During these periods, both Sorafenib and Camrelizumab were temporarily discontinued for 2 months. Encouragingly, the patient has maintained durable CR since May 2020 to now, with regular CT scans and tumor marker tests surveillance every 6 months. The treatment timeline is shown in Figure 5, and the dynamic change of AFP is in Figure 3.

Discussion

The treatment of HCC has significantly advanced with the introduction of combination therapy using TKIs and ICIs [8]. Despite this progress, patients with super-giant HCC and portal vein invasion typically face poor prognoses. This case report presents a super-giant HCC patient with portal vein invasion who achieved long-term CR and a 5-year recurrence-free survival following hepatectomy and subsequent treatment of Sorafenib plus Camrelizumab.

First, targeted immunotherapy has dramatically improved the feasibility and effectiveness of hepatectomy for patients with super-giant HCC beyond current surgical indications. This case demonstrates that in the era of TKIs plus ICIs, patients with super-giant HCC can achieve complete tumor remission and long-term recurrence-free survival after hepatectomy. In generally, patients with HCC tumors larger than 10 cm have poorer prognoses compared to those with smaller tumors. Within 5 years after liver resection, the recurrence rate can be as high as 84.9%, and the overall survival rate as low as 34.0% [9]. However, for patients with giant HCC undergoing TACE, the progression-free survival is only about 9.5 months, and overall survival ranges from 10.6 to 19.3 months [10]. Due to the large size of super-giant HCC, these patients are at high risk for various complications following TACE. As a result, systemic therapy remains the most favorable treatment option [2]. Currently, TKIs combined with ICIs is considered the first-line adjuvant therapy for advanced HCC at preoperative or postoperative. However, as demonstrated in the COSMIC-312 study, not all combination regimens achieve overall survival benefits [11]. Therefore, exploring new combination treatment regimens that extend overall survival for super-giant HCC patients is essential. Sorafenib, a multikinase inhibitor, promotes apoptosis, reduces angiogenesis, and inhibits tumor progression. Before

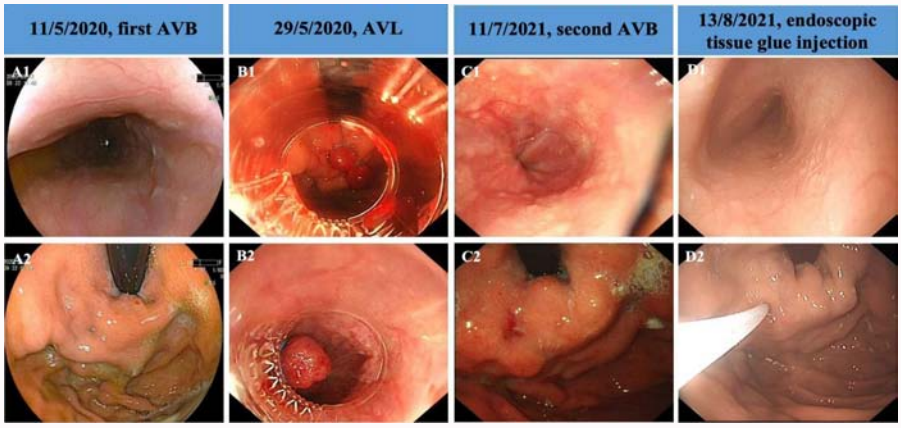

Figure 4: After two episodes of acute esophageal-gastric variceal bleeding (AVB), the upper gastrointestinal endoscopy revealed mild esophagogastric varices without red color signs. The patient was subsequently treated with Esophageal Variceal Ligation (EVL) and endoscopic cyanoacrylate injection.

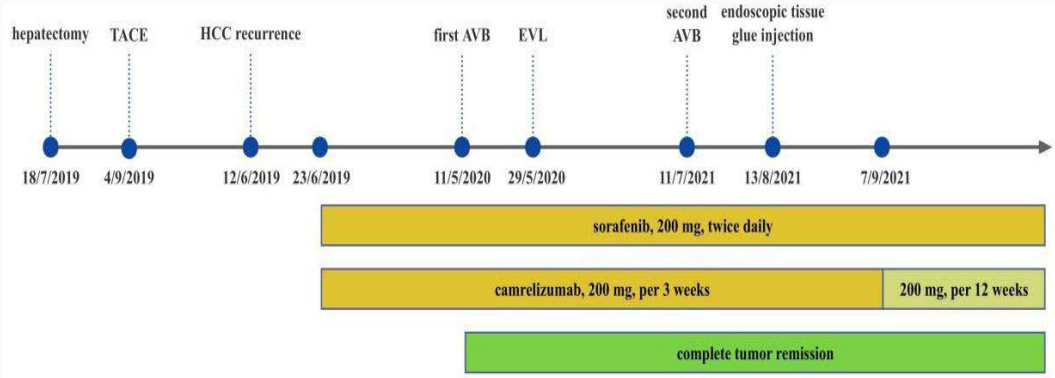

Figure 5: The whole treatment timeline. AVB: Acute esophageal-gastric Variceal Bleeding; EVL: Esophageal Variceal Ligation.

2020, it was the only effective first-line treatment for HCC patients and is still widely used in liver cancer treatment. Camrelizumab, a humanized high-affinity PD-1 monoclonal antibody, has shown safety and efficacy in HCC. The safety and efficacy of the Sorafenib and Camrelizumab regimen have been confirmed by some studies. In a 2022 retrospective study, recurrence-free survival was significantly extended to 10.2 months in the group receiving Sorafenib combined with Camrelizumab, compared to 6.1 months in the Sorafenib monotherapy group [7]. Similarly, another study demonstrated that combining Camrelizumab and Sorafenib with TACE can improve the survival rate of patients with HCC. Similarly, another research also demonstrated that Camrelizumab plus Sorafenib combined with TACE can improve the survival rate of patients with HCC [6]. Despite these advances, reports of patients with super-giant HCC and portal vein invasion achieving long-term CR through TKIs and ICIs treatments are still rare. This case suggests that hepatectomy can maximally reduce tumor burden, thereby increasing the sensitivity and effectiveness of subsequent TKIs plus ICIs.

Second, in the era of targeted immunotherapy, managing portal hypertension in HCC patients is crucial. This patient experienced bleeding twice due to gastroesophageal varices during systemic therapies, indicating that the Barveno VII criteria may not be appropriate for predicting esophagogastric varices or bleeding in HCC patients with compensated cirrhosis undergoing TKIs and ICIs treatment. Based on Barveno VII criteria, patients with LSM ≤ 15 kPa and PLT ≥ 150×10^9/L can be diagnosed without clinically significant portal hypertension and avoid endoscopy [12]. However, HCC can worsen portal hypertension and increase bleeding risk related to the development of arteriovenous shunts, structural liver changes, and portal vein tumor invasion [13]. In recently, there is growing concern about the potential for targeted immunotherapy drugs to increase gastrointestinal bleeding in HCC patients. VEGF receptor inhibitors are believed to increase bleeding risk by reducing endothelial cell regenerative capacity, inhibiting angiogenesis, and decreasing collateral vessel proliferation [14-16]. This patient was not advised to undergo screening endoscopy initially because his LSM was ≤ 15 kPa and PLT was ≥ 150×10^9/L according to Baveno II criteria. However, he experienced esophagogastric variceal bleeding twice despite an excellent tumor response and stable liver function, with no further bleeding after endoscopic therapy. Therefore, our report suggests that the Barveno VII criteria are inadequate for screening for portal hypertension in HCC patients underwent TKIs and ICIs treatment. We recommend that HCC patients, even with LSM ≤ 15 kPa and PLT ≥ 150×10^9/L, undergo screening endoscopy before starting targeted immunotherapy. To ensure continuous and effective targeted immunotherapy, regular gastroscopy intervals should be shortened during treatment, and necessary prophylactic treatment of esophagogastric varices should be actively pursued.

Finally, determining the optimal duration and discontinuation strategy for targeted immunotherapy drugs remains challenging for clinicians. HCC patients typically discontinue targeted immunotherapy due to disease progression, drug resistance, or serious adverse events such as hand-foot skin reactions, diarrhea, liver dysfunction, and upper gastrointestinal hemorrhage [17]. With

the advent of targeted immunotherapy, CR is possible but rare in advanced HCC patients, with rates as low as 1.3% in the targeted therapies group and 2.7% in the immune checkpoint inhibitors group [18,19]. However, for patients who achieve CR, there are no guidelines on the optimal duration of TKIs and ICIs [20]. Additionally, it remains uncertain whether HCC patients will still benefit from their original treatment regimen if the tumor recurs after discontinuation. Indefinite-duration treatment could reduce recurrence but might also lead to significant economic waste and the accumulation of drug toxicity. In this case, Sorafenib plus a PD-1 inhibitor, has been administered continuously for over 5 years, except periods of variceal bleeding, with favorable outcomes. The emerging issue for clinicians is determining when and how to safely discontinue the treatment of Sorafenib plus Camrelizumab, a topic worth discussing and investigating.

Overall, the combination of TKIs and ICs is a potentially effectiveness and feasibility for super-giant HCC patients with portal vein invasion after hepatectomy, although beyond current surgical indications. This surgery may significantly reduce tumor burden, enhance systemic therapy efficacy. However, extensive use of TKIs plus ICIs combination therapy raises two critical issues: How to perform endoscopic screening varices and manage portal hypertension in HCC patients, and how to determine the optimal treatment duration of TKIs and ICIs in long-term CR HCC patients. Further research is needed to address these challenges and improve patient outcomes.

Author Contributions

X.Z. prepared and wrote the manuscript. W.J. and L.S. drafted and corrected the figures. H.X. collected the data. J.W., H.L., W.S., C.G., and X.W. contributed to the design of the manuscript. H.D. critically revised and edited the manuscript content. All authors have read and agreed to the published version of the manuscript.

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