



# Complete response by patients with advanced hepatocellular carcinoma after combination immune/targeted therapy and transarterial chemoembolization: two case reports and literature review

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**Background:** Effective treatment for patients with advanced unresectable hepatocellular carcinoma (HCC) is severely lacking. The most common clinical treatments include a combination of immunotherapy, molecular targeted agents, and transarterial chemoembolization (TACE). The combinations of therapies most likely to lead to complete recovery are unclear. The cases in this study were treated with TACE therapy and radiofrequency ablation followed by massive tumor antigen release as a way to enhance the effect of immune and targeted therapy, and TACE therapy followed by combination with programmed death 1 (PD-1) inhibitors and molecular targeted drugs may achieve better efficacy. We share two cases of advanced HCC patients who achieved complete response (CR) after treatment with PD-1 inhibitor combined with Lenvatinib and TACE and radiofrequency ablation to provide a reference for the treatment choice of advanced HCC patients.

**Case Description:** We report two case studies of two Chinese men with advanced primary HCC (Barcelona Clinic Liver Cancer stage C) involving portal vein carcinoma thrombosis and Child-Pugh A liver function. Complete regression of the lesions and thrombosis was reached after TACE and radiofrequency ablation, followed by the combination of PD-1 inhibitor and Lenvatinib.

**Conclusions:** We speculate that patients with advanced HCC with Child-Pugh A liver function may have better efficacy if they are treated with TACE and radiofrequency ablation followed by tumor necrosis and release of intratumoral antigens to achieve the effect of intensive immune and targeted therapy, and then sequential application of PD-1 inhibitors combined with molecular targeted drugs for conversion therapy. Further stimulate the body's immunity, so that the patient may reach CR. However, because surgical resection pathology was not performed, it is not clear whether pathological CR was achieved and the future prognosis remains to be further observed.

**Keywords:** Hepatocellular carcinoma (HCC); immunotherapy; targeted therapy; case report

Submitted Dec 01, 2021. Accepted for publication May 09, 2022.

doi: 10.21037/tcr-21-2691

**View this article at:** <https://dx.doi.org/10.21037/tcr-21-2691>

## Introduction

Hepatocellular carcinoma (HCC) leads to the third highest annual cancer-related mortality rate worldwide (1). Clinical manifestations of HCC usually do not appear until the middle or late stages of disease progression. As many as half of patients are first diagnosed when the cancer is already at an advanced stage. The preferred treatment for early-stage HCC is surgical resection, while effective treatment for advanced HCC is still lacking (2).

In recent years, the emergence of many new immunotherapies, such as immune checkpoint blockade therapy, has improved the treatment of advanced HCC (3). In particular, inhibitors targeting the interaction between T-cells and tumor cells mediated by the receptor programmed death (PD)-1 and its ligand PD-L1 have received attention. However, immune checkpoint inhibitors may not always be effective, reflecting the complex relationship between the tumor microenvironment and the immune response, which highlights the need to clarify under what circumstances such therapy works best (4). Combining PD-1/PD-L1 inhibitors with molecularly targeted drugs may drastically improve treatment of advanced HCC (5,6). Several strategies are already under investigation: the “dual immune regimen” combining Nivolumab with Ipilimumab, the “cola combination” combining Pembrolizumab with Lenvatinib, and the “A+T regimen” combining Atezolizumab with Bevacizumab. These combinations have improved the objective response rate of advanced HCC. It may also be possible to increase the efficacy of immunotherapeutic agents synergistically by first performing transarterial chemoembolization (TACE) (7), which can induce the release of large amounts of tumor antigens (8). This may improve patient outcomes and prognosis.

Here we report two patients diagnosed with advanced unresectable HCC who underwent local treatment modalities, such as TACE and radiofrequency ablation, and then achieved CR after combining immune and molecular targeted-therapies. Furthermore, we summarize the relevant literature on combination therapies to improve the clinical understanding of HCC and provide a basis for clinical treatment plan. We present the following article in accordance with the CARE reporting checklist (available at <https://tc.amegroups.com/article/view/10.21037/tcr-21-2691/rc>).

## Case presentation

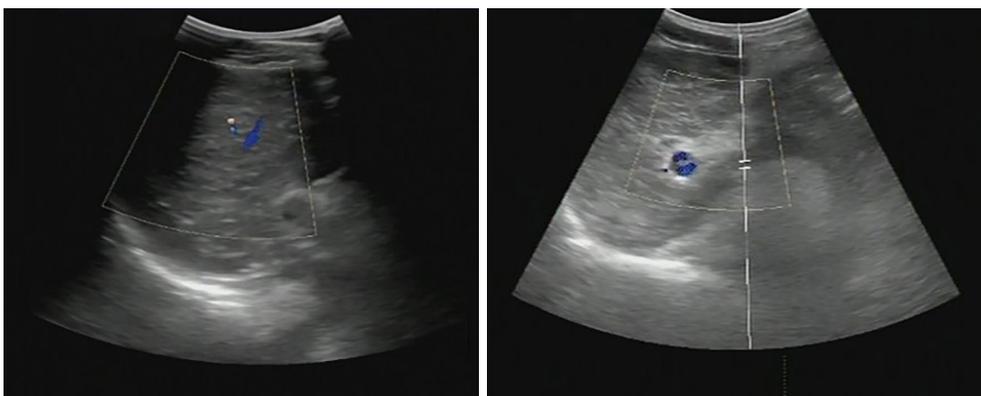
All procedures performed in this study were in accordance

with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

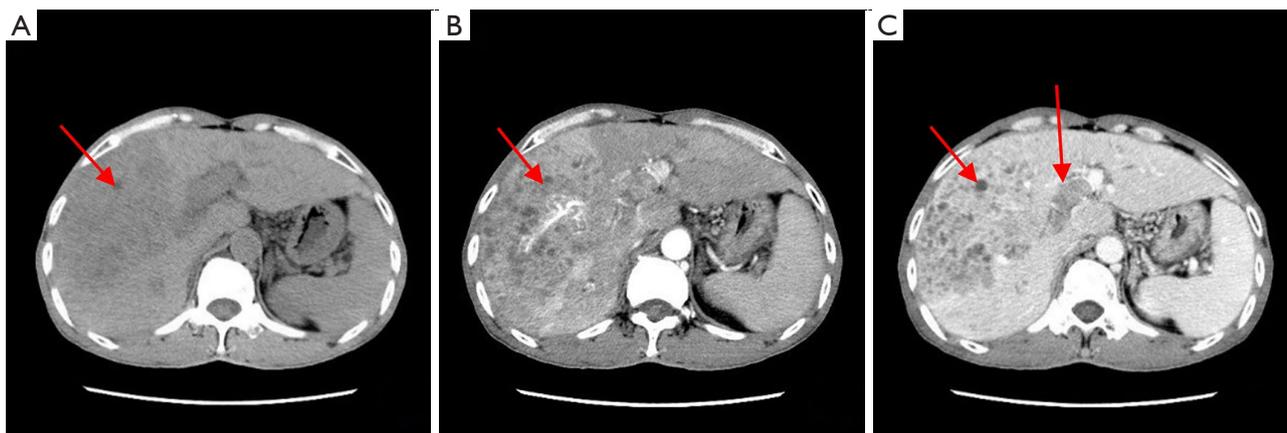
### Case 1

On February 20, 2020 a 47-year-old Chinese man was admitted to our hospital complaining of right upper abdominal pain for more than 10 days. The patient had a previous history of Hepatitis B and had no family history of HCC. Physical examination: light pressure pain in the right upper abdomen, failure to palpate the liver, and the rest of the physical examination was unremarkable. Blood was taken and the following parameters were measured: alpha-fetoprotein (AFP), 388.89 ng/mL; hepatitis B DNA,  $2.99 \times 10^5$  IU/mL; total bilirubin, 33.9  $\mu$ mol/L; albumin, 34.8 g/L; prothrombin time, 13.3 sec; and Child-Pugh liver function, A. Ultrasonography of the abdomen showed a lesion in parenchyma on the right lobe of the liver (*Figure 1*). Computed tomography (CT) of the upper abdomen showed a low-density mass in the right lobe of the liver, with an area of  $8.6 \times 13.3$  cm<sup>2</sup>, and enhanced CT showed a “fast-in/fast-out” pattern, with extensive filling defect areas in the left and right branches of the portal vein and trunk (*Figure 2A-2C*).

The patient was diagnosed with HCC in Barcelona Clinic Liver Cancer (BCLC) stage C. The patient was treated with a combination of Lenvatinib (8 mg QD) and anti-PD-1 drugs (1 cycle every 21 days). After two cycles of targeted therapy and immunotherapy, the AFP level increased to 954.87 ng/mL. CT of the upper abdomen showed a slightly reduced hypodense mass in the right lobe of the liver, with an area of about  $7.2 \times 12.4$  cm<sup>2</sup>; the left and right branches of the portal vein and the main trunk showed a slightly reduced area of filling defect (*Figure 3A-3C*). After four cycles of immunotherapy, the AFP level fell to 19.07 ng/mL, and the hypodense mass shrank to  $5.2 \times 9.2$  cm<sup>2</sup>; the filling defect area of the left and right branches of the portal vein and the trunk was smaller and less dense than before (*Figure 3D-3F*). After six cycles of therapy, upper abdominal CT showed lesion in the right lobe of the liver measured  $5.3 \times 8.0$  cm<sup>2</sup> (*Figure 3G-3I*). After eight cycles, the AFP level was lower still, at 10.14 ng/mL, as was the lesion, at  $4.2 \times 6.3$  cm<sup>2</sup> (*Figure 3J-3L*). Throughout, the patient's



**Figure 1** Abdominal ultrasound images of Case 1 at admission.



**Figure 2** Computed tomography of the right lobe of the liver in Case 1 before treatment: (A) plain phase, (B) arterial phase, (C) venous phase. The red arrows indicate the tumor and the portal vein tumor thrombus.

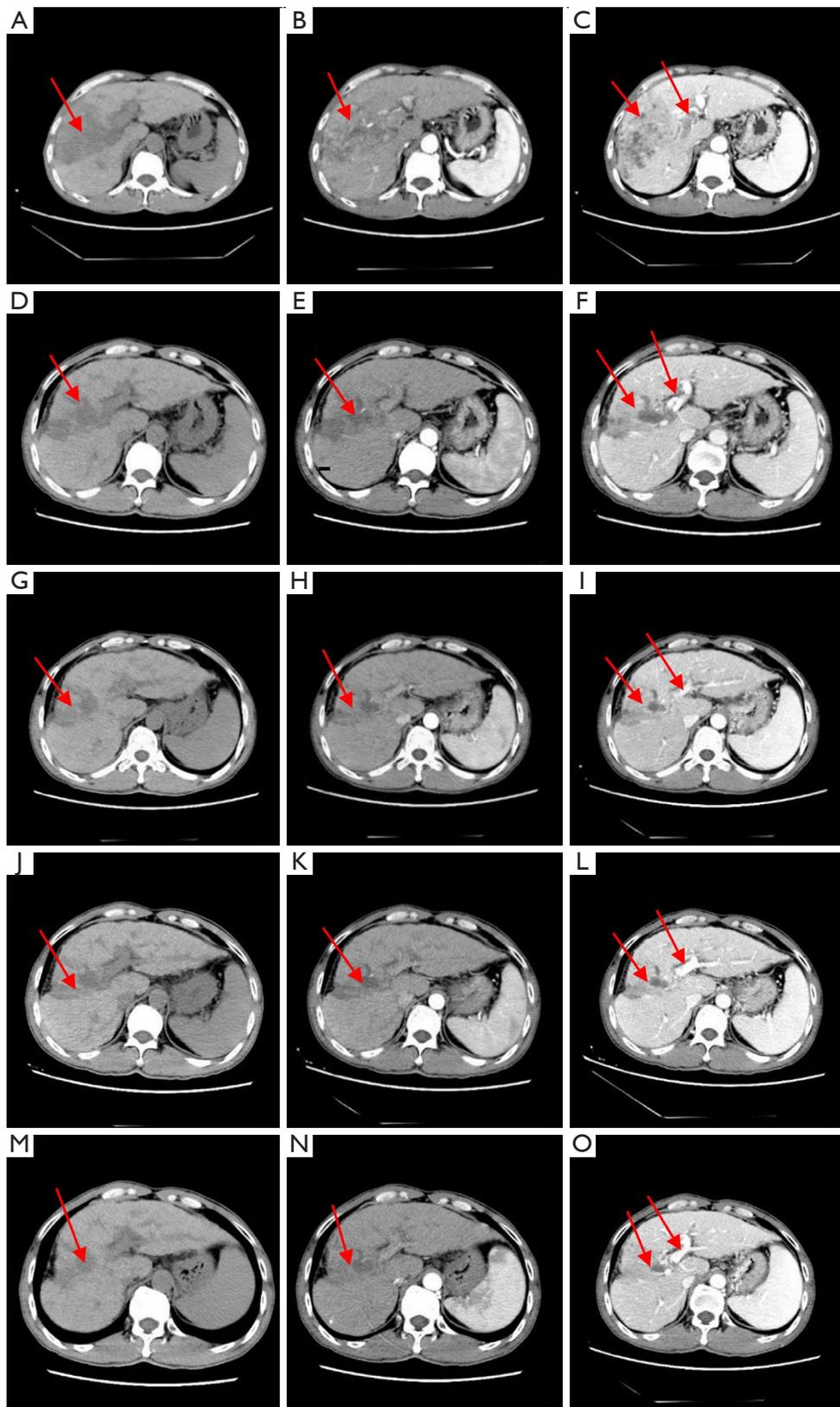
liver function remained at Child-Pugh grade A.

After a comprehensive analysis of the patient's condition, TACE was performed, after which the patient underwent another four cycles of targeted therapy and immunotherapy. In the end, the patient's AFP level dropped to 7.48 ng/mL, the lowest level since admission, and CT of the upper abdomen showed a lesion in the right lobe of the liver measuring only 3.8×3.6 cm<sup>2</sup> (Figure 3M-3O). No active tumor lesion was found by embolization. We have used a timeline figure to summarize the clinical characteristics, treatment and prognosis of the patient in case 1 (Figure 4).

### Case 2

On November 7, 2016, a 67-year-old Chinese man was hospitalized at Guangxi Medical University Cancer Hospital

with right upper abdominal discomfort that had lasted more than 20 days. The patient had a previous history of Hepatitis B and had no family history of HCC. Physical examination: light pressure pain in the right upper abdomen, failure to palpate the liver, and the rest of the physical examination was unremarkable. Laboratory tests found AFP of 7.7 ng/mL, undetectable hepatitis B DNA, total bilirubin of 14.9 μmol/L, albumin of 44.3 g/L, prothrombin time of 10.9 sec, and Child-Pugh liver function grade of A. Abdominal ultrasonography showed a substantial lesion in the liver (Figure 5), and magnetic resonance imaging of the liver showed an abnormal signal mass in the left outer lobe of the liver and an abnormal signal nodule in the right lobe of the liver. The larger mass in the left lobe was 6.4×3.3 cm<sup>2</sup>. Enhanced CT showed “fast-in/fast-out”; the right branch of the portal vein was close to the mass, while the right branch



**Figure 3** Computed tomography of the upper abdomen of Case 1 during combined immuno/targeted therapy. The red arrows indicate the tumor and the portal vein tumor thrombus.

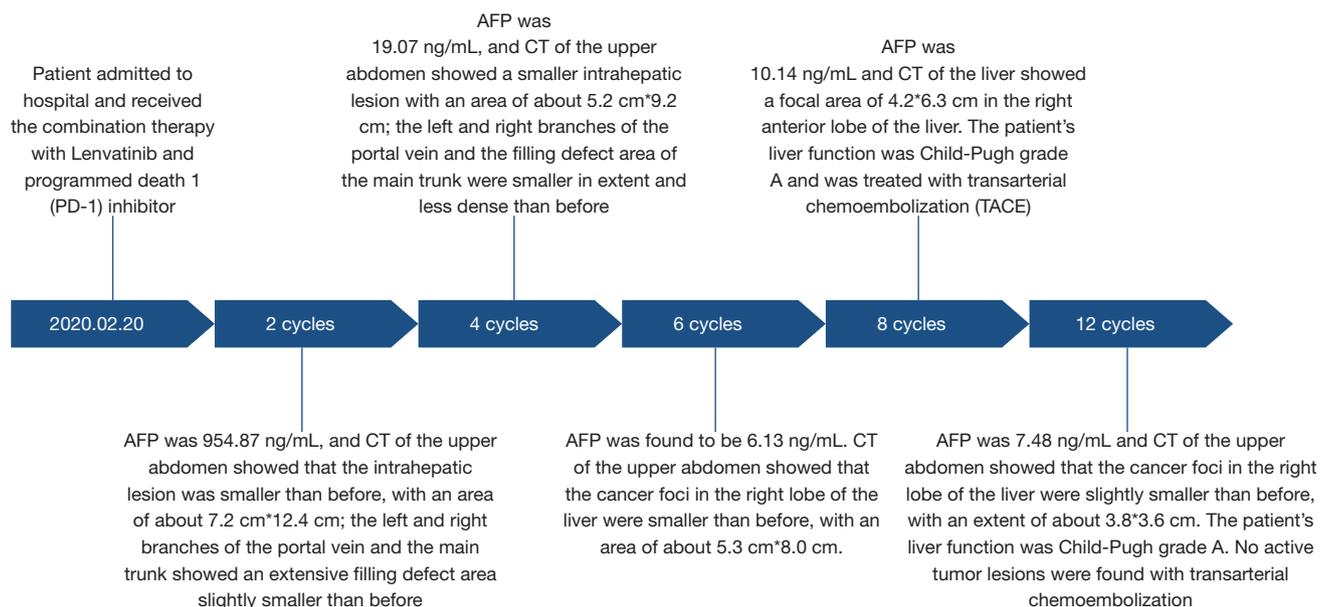


Figure 4 Timeline of patient history development in Case 1.

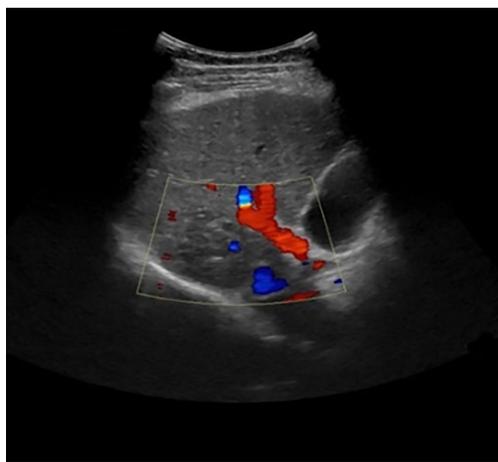


Figure 5 Color Doppler ultrasonography of the abdominal ultrasound images of Case 2 at admission.

of the portal vein was invaded (Figure 6).

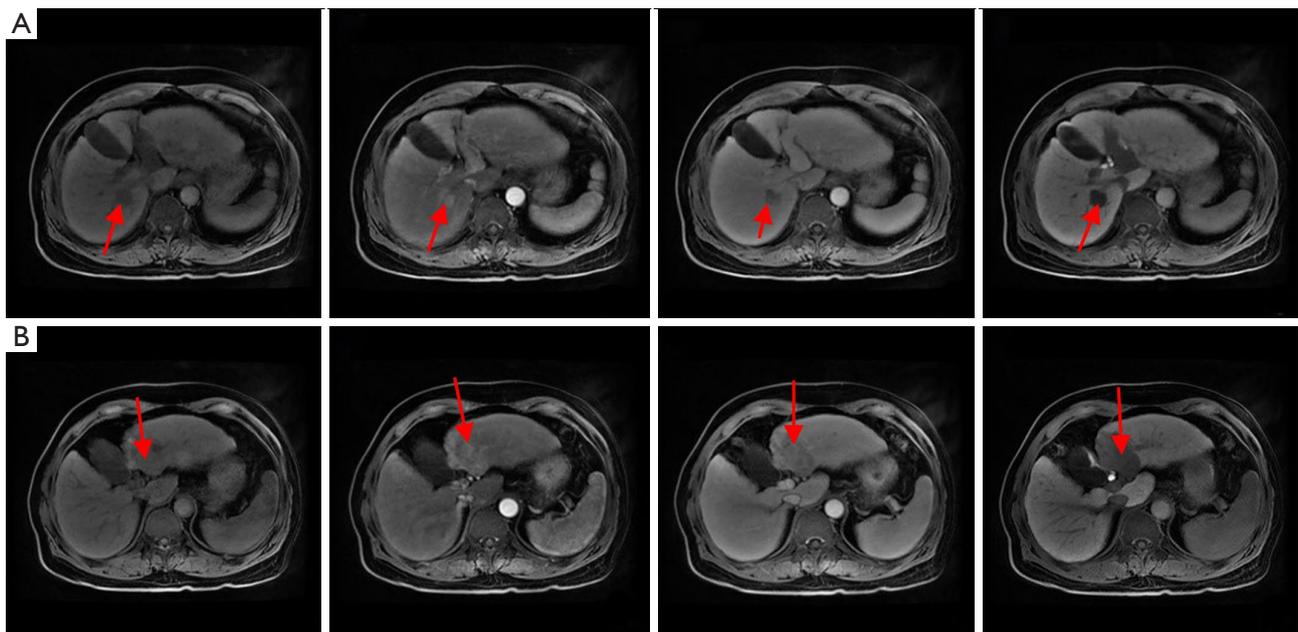
The patient was diagnosed with HCC in BCLC stage C. At one week after admission, the patient was treated with TACE, followed one week later by radiofrequency ablation. After these interventions, the liver lesion measured 5.5\*2.8 cm<sup>2</sup> and showed a dense shadow of iodine oil deposition; the swelling shadow in the right posterior lobe of the liver was larger than at admission, measuring 4.5\*3.8 cm<sup>2</sup> (Figure 7). Hepatectomy was performed on the left lobe of the liver at

two weeks after admission.

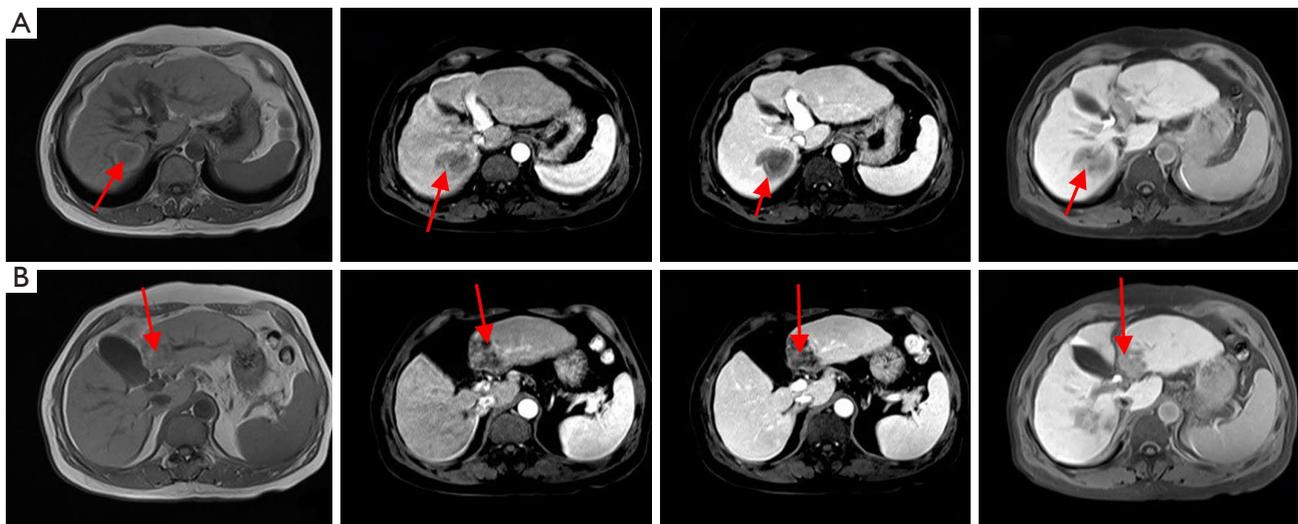
Postoperative pathology showed a liver mass with nodular cirrhosis and extensive nodular necrosis covering an area of 6\*3.5\*3 cm<sup>3</sup>, with clear borders. No residual tumor tissue, definite vascular carcinoma thrombi or satellite nodules were observed. The resection edge was negative for tumor cells. Immunohistochemistry failed to detect CK7, CK19, HBsAg or HBcAg; glypican-3 reactivity was borderline; and Ki67 expression was around 5%. Tissue was positive for p53. The pattern of CD34 expression indicated normal distribution of blood vessels.

From 2017 to 2020, the patient returned to the hospital for regular bi-monthly check-ups, and no significant elevation of AFP was observed. During this period, however, the patient experienced multiple recurrences of intrahepatic lesions and was treated by radiofrequency ablation and anhydrous alcohol injection. Multiple new foci were seen at the junction of the left and right lobes, of which the largest measured 7.8\*4.6 cm<sup>2</sup>. Additionally, the right anterior branch of the portal vein showed cancerous thrombosis (Figure 8A-8D).

Combination therapy with Lenvatinib (8 mg QD) and anti-PD-1 drugs (1 cycle every 21 days) was initiated on July 17, 2020. After 3 cycles of targeted therapy and immunotherapy, AFP was 2.37 ng/mL and MRI of the liver showed shrinkage of the recurrent foci at the junction of



**Figure 6** Magnetic resonance imaging of the liver of Case 2 at admission: (A) right lobe, (B) left lobe. The red arrows indicate the tumors.



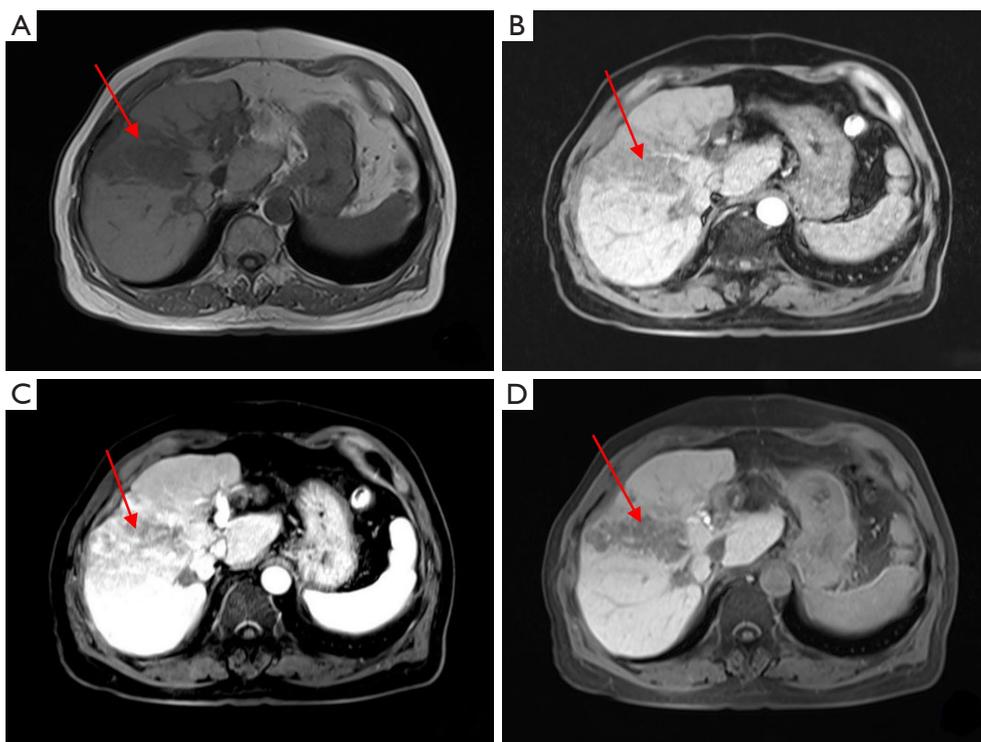
**Figure 7** Pre-operative magnetic resonance imaging of the liver of Case 2: (A) right hepatic lobe, (B) left hepatic lobe. The red arrows indicate the tumors.

the left and right lobes of the liver; the larger focus in the junction of the left and right lobes measured approximately  $6.8 \times 3.1 \text{ cm}^2$  (Figure 9A-9C). After six and nine cycles of therapy, the recurrent foci at the junction of the left and right lobes of the liver continued to shrink, based on MRI (Figure 9D-9I). After 12 cycles, AFP was 2.27 ng/mL and MRI showed complete regression of the intrahepatic lesions

(Figure 9J-9L). We have used a timeline figure to summarize the clinical characteristics, treatment and prognosis of the patient in case 2 (Figure 10).

## Discussion

HCC has an insidious onset and most patients have no



**Figure 8** Magnetic resonance imaging of the mass in the right hepatic lobe before targeted combined immunotherapy in Case 2: (A) plain phase, (B) arterial phase, (C) portal phase, (D) hepatobiliary phase. The red arrows indicate the tumor.

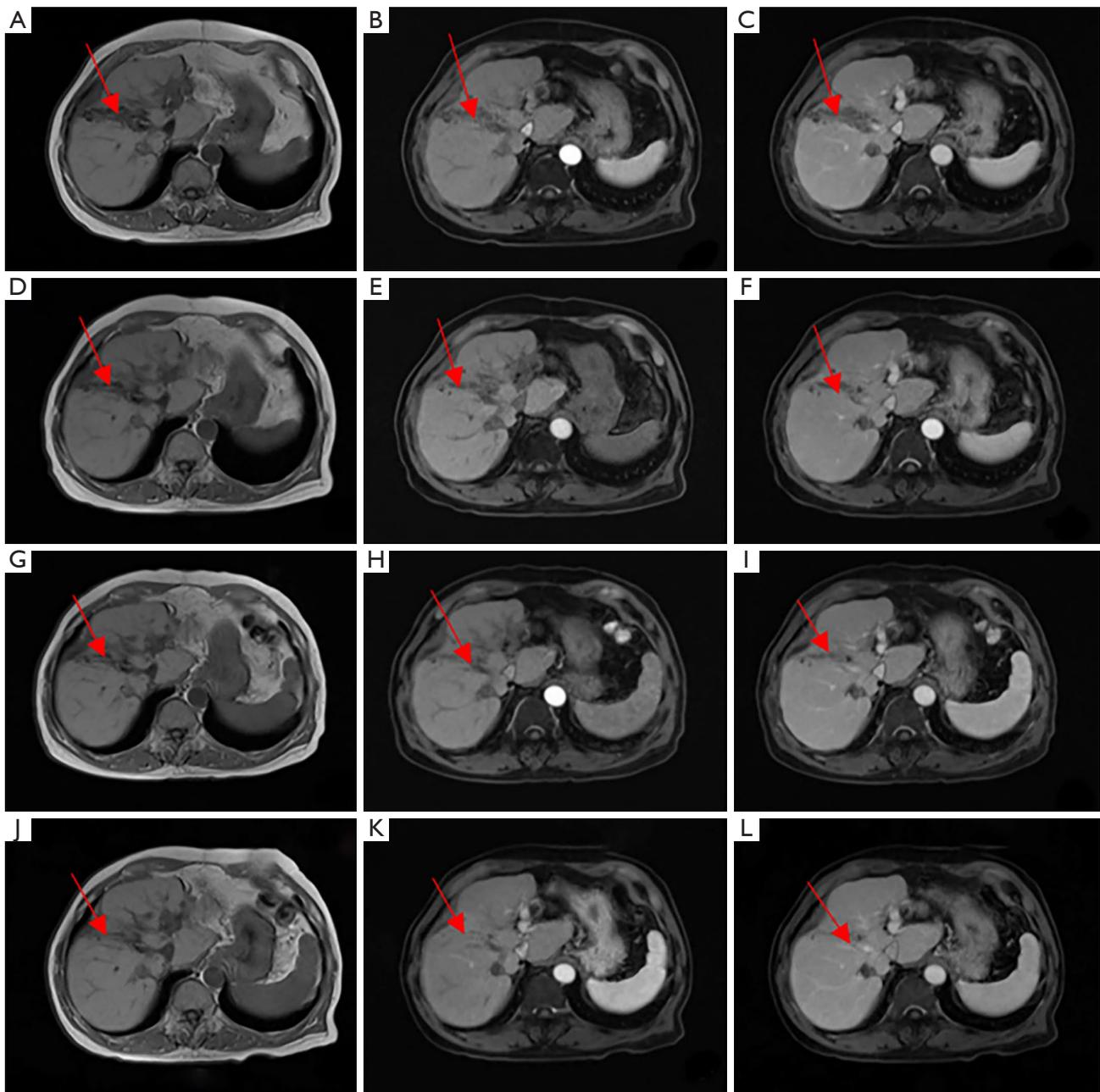
clinical symptoms. Patients with advanced HCC show median survival times of only 3.0 to 5.7 months, depending on whether they have hepatic macrovascular invasion, extrahepatic metastases, or both. The 1-year survival rate is only 12.0% to 38.3% (9-14). The lack of effective therapeutic measures for advanced HCC often means very poor prognosis, but immune checkpoint inhibitors combined with anti-angiogenic targeted drugs have recently become popular for treating unresectable advanced HCC and may improve outcomes. Our cases illustrate that such therapy may be particularly effective if performed after TACE.

PD-1 is an immunosuppressive molecule strongly expressed on tumor-specific T cells (15), while PD-L1 is expressed on tumor cells as an “immune-adaptive mechanism” to evade anti-tumor responses (16). When PD-1 is activated by its ligand, PD-L1, it initiates a series of responses that suppress T-cell activity and promote tumor cell growth (17), PD-1/PD-L1 inhibitors are drugs that block the interaction of PD-1 and PD-L1, restoring T-cell activity and the individual immune system’s ability to kill tumor cells (18). Several PD-1 inhibitors have

shown efficacy in clinical trials, including Nivolumab (19), approved by the US Food and Drug Administration; Pembrolizumab (20); and Camrelizumab, which has been approved by the Chinese National Medical Products Administration (21).

Sorafenib and Lenvatinib are molecularly targeted anti-angiogenic drugs that prolong the survival of patients with advanced HCC. While sorafenib has historically been the only systemic drug widely used worldwide against advanced disease (22), Lenvatinib has recently emerged as a potentially better alternative (23,24); the drug has shown strong therapeutic effects against not only HCC tumors but also portal vein cancer thrombosis.

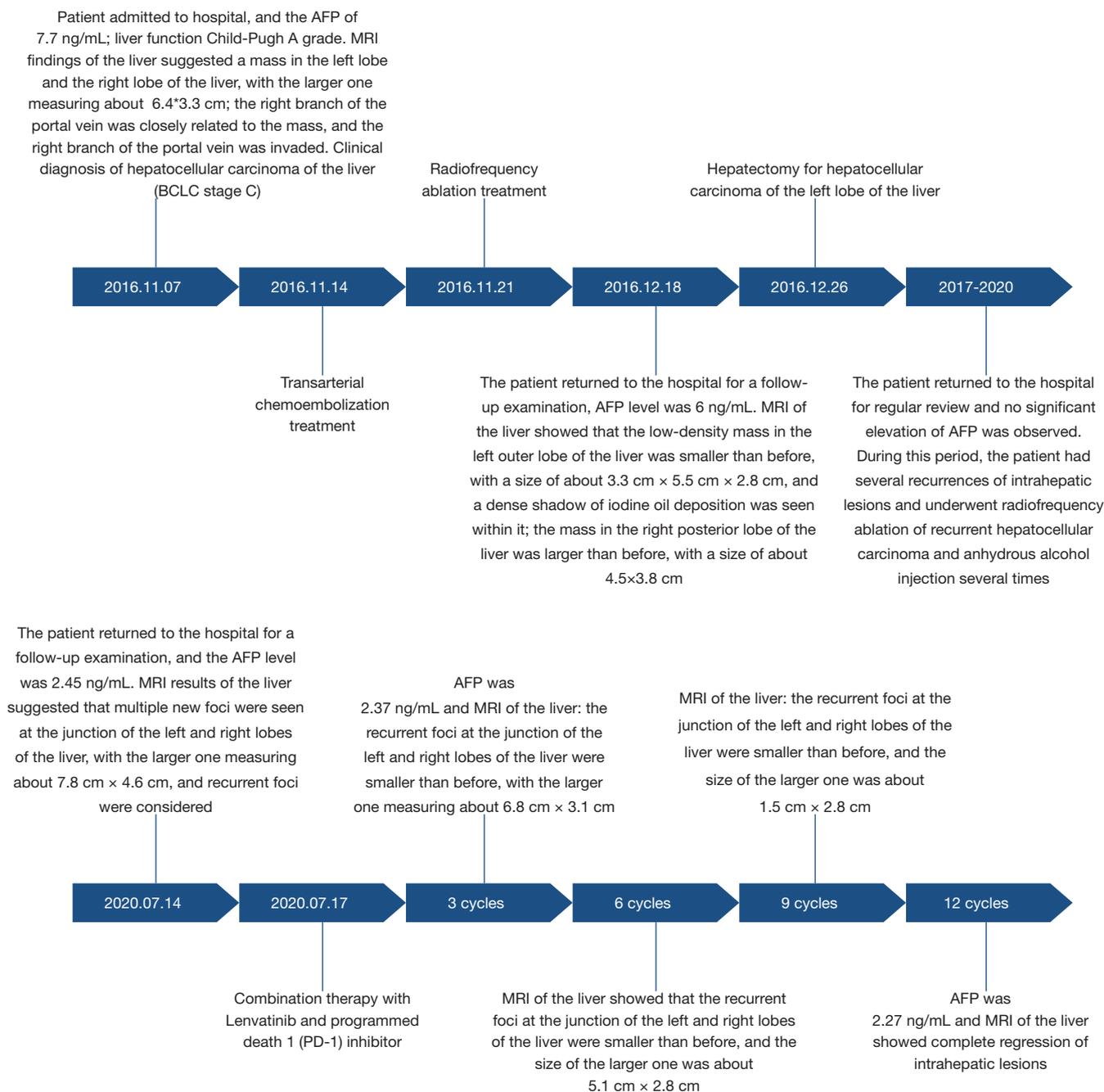
Nevertheless, monotherapies with either immunotherapeutic agents alone or molecularly targeted drugs alone are not entirely satisfactory (6). Combining the two approaches has shown the potential to achieve synergistic effects in several clinical trials, such as the combination of Lenvatinib and Pembrolizumab (25), Lenvatinib and Nivolumab (26), Camrelizumab and Apatinib (27), Atezolizumab and Bevacizumab (28), Sintilimab and Bevacizumab (29).



**Figure 9** Magnetic resonance imaging of the liver of Case 2 during combined immuno/targeted therapy. The red arrows indicate the tumor.

TACE can induce the release of local inflammatory factors and neoantigens (8), which induces a large number of T cells to migrate to the lesion site. This results in high expression of PD-1 molecules on the surface of the T cells, providing more targets for PD-1 inhibitors (30,31). Thus, several trials are evaluating the combination of TACE with immune checkpoint

inhibitors. One trial, for example, found that combining TACE with Camrelizumab led to Objective Response Rates above 50% after the therapy (32). Ongoing are a multicenter, nonrandomized, pilot study (NCT03143270) on the safety and feasibility of drug-loaded microspheres for TACE in combination with Nivolumab (33), as well as a phase I/II trial on safety and efficacy of TACE



**Figure 10** Timeline of patient history development in Case 2.

followed by the PD-1 inhibitor Pabrolizumab (34). Radiofrequency ablation can also release neoantigens in a similar manner as TACE (35), and therefore we applied both TACE and ablation to our patients.

Given the heterogeneity of HCC, the combination of TACE and immune/targeted therapies that works best

likely depends on individual patient characteristics. We suspect that the relatively good outcomes in our two cases reflect the fact that both were treated with TACE, which potentiated anti-PD-1 therapy; both showed high PD-1 expression, which is associated with better response to anti-PD-1 therapy (36); and both exhibited Child-Pugh A liver

function, which may also be associated with better response to anti-PD-1 therapy (37). Interestingly our cases showed low or negligible AFP levels, suggesting that this level may not correlate with prognosis.

TACE may not be suitable for patients whose HCC involves portal vein trunk invasion because of the possibility of liver failure (38). Although both our patients showed such invasion, they also showed good blood flow and abundant collateral circulation, which may have contributed to good outcomes. These experiences are consistent with a previous report that TACE can be safe and effective in the presence of abundant collateral circulation around the portal vein (38).

During the treatment process, we continuously use the treatment modalities that promote the release of tumor antigens, such as TACE, radiofrequency ablation and other local treatments, so that the tumor antigens can be released as much as possible to strengthen the effect of immune and targeted therapy. We speculate that patients with advanced HCC with Child-Pugh grade A liver function may have better efficacy if they are treated with TACE and radiofrequency ablation first, followed by tumor necrosis and release of intratumor antigens to enhance the effect of immune and targeted therapy, and then sequential application of PD-1 inhibitors combined with molecular targeted drugs to transform therapy. stimulate the body immunity, so that patients may reach CR.

There are still shortcomings in this study: (I) pathological examination without surgical resection could not clarify whether pathological CR was achieved. (II) The future prognosis remains to be further observed. Although the patient achieved clinical CR with PD-1 inhibitor combined with Lenvatinib after TACE and radiofrequency ablation treatment, the duration of this treatment modality to maintain the patient's CR efficacy and the duration of continued use of targeted and immunologic drugs after achieving clinical CR are still not clear. They are still in the stage of clinical exploration and need long-term observation and research.

In summary, the treatment of advanced HCC adopts a multi-modal combination therapy model, and individualized treatment plans should be developed according to individual conditions to improve the quality of life and maximize patient benefit. We report two cases of HCC patients who received TACE and radiofrequency ablation followed by sequential application of PD-1 inhibitors combined with molecularly targeted drugs for conversion therapy and achieved clinical CR. With these two cases, we speculate

that for patients with advanced HCC who have Child-Pugh grade A liver function, lesions confined to the hemi-hepatic, tumors that are diffuse but fused into a single lesion, abundant peritumor blood flow, and portal vein carcinoma thrombosis staging Patients with advanced HCC not exceeding type III, after receiving TACE therapy and radiofrequency ablation, intratumoral antigens are released to achieve intensive immune and targeted therapy, and then PD-1 inhibitor combined with Lenvatinib conversion therapy is given with potentially better efficacy. At the same time, we caution that we did not perform histopathology on surgical specimens to determine whether pathological CR was achieved in our patients, nor did we assess outcomes in the long term. Future studies should also aim to optimize timing and duration of the different modalities in the combination therapy.

### Acknowledgments

We would like to thank Chapin Rodríguez for his help in polishing our paper.

*Funding:* None.

### Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2691/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2691/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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**Cite this article as:** Nong X, Zhang YM, Liang JC, Xie JL, Zhang ZM. Complete response by patients with advanced hepatocellular carcinoma after combination immune/targeted therapy and transarterial chemoembolization: two case reports and literature review. *Transl Cancer Res* 2022;11(8):2973-2984. doi: 10.21037/tcr-21-2691