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A Case of Successful Transformation of Unresectable Liver Cancer after TACE Combined with Apatinib and Camrelizumab

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KEYWORDS Apatinib. Camrelizumab Injection. Combination Therapy. Hepatectomy. Liver Cancer

ABSTRACT Hepatocellular carcinoma (HCC) is a common malignant tumour of the digestive system with gradual onset, and the survival rate is low in patients with advanced HCC. This case reports a 33-year-old woman diagnosed with right hepatic lobe malignancy with portal vein tumour thrombus. The patient has preoperatively taken transarterial chemoembolization (TACE) combined with Apatinib and Camrelizumab immunotherapy, which led to a significant reduction in the volume of the tumour and a reduction in the quantity of tumour markers. The patient was treated by right hemihepatectomy after evaluation, and postoperative pathological examination showed that the patient's hepatocellular carcinoma with portal vein tumour thrombus was completely necrotic. TACE combined with Camrelizumab immunotherapy was continued after operation. As follow-up, tumour markers continued to decrease, and no tumour recurrence or distant metastasis have taken place. Data of the case suggests that combined transformation therapy could be a boon for advanced unresectable HCC patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for the 5th largest number of cases globally, and is one of the growing outbreaks of health problems in developing countries (Bray et al. 2018). Researchers have been developing new approaches for treatment, such as using multimodality therapy for massive HCC (Lin et al. 2022). In clinical experience, the formation of portal vein tumour thrombosis (PVTT) in hepatocellular carcinoma is one of the most important challenges faced by clinical and scientific researchers (Mähringer-Kunz et al. 2019).

At present, surgical resection is still the most common method used for treating HCC. However, the opportunity for surgical resection for patients with intermediate and advanced liver cancer is basically lost at the time of their diagnosis. Another HCC treatment method known as transarterial chemoembolization (TACE) has emerged in recent years (Silva et al. 2017; Chung et al. 2021; Ghanaati et al. 2021). TACE can block tumour blood supply and accumulate high concentrations of chemotherapeutic drugs locally to maximise the killing (cytotoxic) effect on tumour cells (Chen et al. 2019). Nowadays, TACE is one of the commonly used non-surgical treatment methods for HCC in China (An et al. 2019). The therapeutic effect of TACE combined with Apatinib and Camrelizumab will be demonstrated in this case.

Apatinib mesylate is a novel and selective small-molecule of vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor, which is the second antiangiogenic drug approved by China for treating advanced or metastatic gastric cancer (Scott 2018). Camrelizumab injection (Erica) is a novel humanised immunoglobulin G4 (IgG4) monoclonal antibody (mAb) (Markham and Keam 2019), which can be used to block PD-1 immune checkpoint signalling (Guzik et al. 2019). On 29 May, 2019, Camrelizumab was granted official approval by the National Medical Products Administration (NMPA) for relapsed or refractory classical Hodgkin lymphoma (cHL) after at least second-line systemic therapy (Markham and Keam 2019). Combination therapies may show promising synergistic efficacy for advanced HCC. There is evidence that angiogenesis and immunosuppression frequently occur simultaneously in a tumor microenvironment. Antiangiogenic agent combined with immunotherapy may balance the tumor

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microenvironment and enhance treatment response (Ribatti et al. 2021).

So far, rare cases have reported the efficacy and safety of TACE combined with Apatinib and Camrelizumab injection in HCC. The researchers reported here a successfully treated patient with primary massive HCC who underwent pre- and post-operative TACE treatment and achieved a pathologic complete response (pCR).

Objectives

The purpose of this study was to explore the case report of a 33-year-old woman diagnosed with right hepatic lobe malignancy with portal vein tumour thrombus.

METHODOLOGY

The data of this study was collected on 20 July, 2022.

A 33-year-old woman was presented to the outpatient clinic on 6 August, 2020 with mild loss of appetite and occasional nausea. She was found to have a liver tumour and admitted to the researchers' hospital for further treatment.

The patient had intermittent dull pain and discomfort in the right upper abdomen without obvious cause for 6 months. There were no significant aggravating or alleviating factors. She had been consulted at a local hospital and was prompted to have a liver tumor, and there had been no significant changes in weight or physical strength. She had a history of hepatitis B for 10 years without medication or other treatment. She had no previous surgical history. Her father had hepatitis B, and she had no family history of liver cancer.

On 6 August, 2020, the patient underwent contrast-enhanced computed tomography (CT) and physical examination in the hospital. There was no obvious jaundice in the skin and sclera, and no other obvious signs noted. A mass was palpable in the upper abdomen with tenderness on percussion in the liver region. Contrast-enhanced CT scan revealed a mass measuring approximately 11×8 cm, located in the right lobe of the liver, showing an 'arterial wrapping sign' and suggesting a diagnosis of HCC. The right branch of the hepatic artery was embedded in the mass, and the filling defect of the right portal vein was visible (Fig. 1).

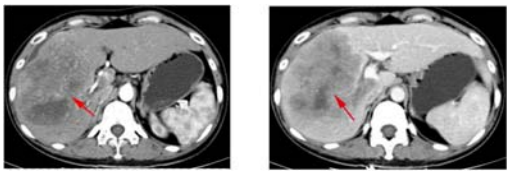

Fig. 1. Preoperative contrast-enhanced CT image. The arrow indicated the tumor lesion.
Source: Author

Laboratory test data showed that the patient was HBsAg positive, HBeAb positive, HBcAb positive, and others negative. The patient's alpha-fetoprotein (AFP) was >200000 ug/L, abnormal prothrombin at 15323 mAU/ml, and Child-Pugh grading at 5 points (stage A). The disease was diagnosed as primary hepatocellular carcinoma with Barcelona Clinic Liver Cancer (BCLC) Stage C. The patient had a large right hepatocellular carcinoma with no indication for surgery (Fig. 1).

After the treatment plan was informed and written consent was obtained from the patient and her family, systematic treatment was initiated. Apatinib targeted therapy was started on 7 August, 2020 (250 mg/day). The patient underwent two TACE treatments in the Department of Interventional Radiology of the hospital on 7 August, 2020, and 8 October , 2020, respectively. Each treatment included slow injection of NS100 ml + 0.75 g fluorouracil into the common hepatic artery for perfusion chemotherapy, and slow injection of drug-loaded microspheres 1 g + epirubicin 60 mg mixed emulsion chemoembolization through the microcatheter superselected tumour feeding artery. The patient received camrelizumab immunotherapy (200 mg intravenously every 3 weeks) at the department from 9 August, 2020 to 27 October, 2020. During combination therapy, the patient experienced a mild decrease in platelet and haemoglobin levels, which improved after symptomatic treatment. Tumour markers decreased during treatment (Table 1) and the patient reported a decrease in abdominal mass. She was discharged on 28 October , 2020.

On 16 November, 2020, the patient came to the hospital again. The examination showed that the AFP of the patient was 15027 ng/mL, and the right lobe of the liver was reduced (7.3 × 7.1 × 7.5 cm) (Fig. 2). Pathological examination on 23 November, 2020 showed partial necrosis of the lesion (Fig. 3). The Child-Pugh score of liver function was 5

Table 1: Changes in tumor markers in patients

Time	*2020/ 8/4*	*2020/ 8/29*	*2020/ 9/14*	*2020/ 10/10*	*2020/ 10/27*	*2020/ 11/16*	*2020/ 11/25*	*2020/ 12/1*	*2020/ 12/28*	*2021/ 1/26*	*2021/ 2/22*	*2021/ 4/10*	*2021/ 10/20*	*2022/ 1/5*	*2022/ 4/5*	*2022/ 7/6*
Alpha-fetoprotein (ug/L)	>200000	45843.1	31344.8	27516	13964.5	15027.4	4115.9	1639.6	118	13.1	1.6	3.9	5.3	13.3	79.6	4.6
Abnormal Prothrombin (mAU/mL)	15323.5	613403.8	68807.11	13003	2384.6	4986.6	1141.96	185.34	24.47	17.42	15.23	24.28	25.98	37.55	31.21	27.38

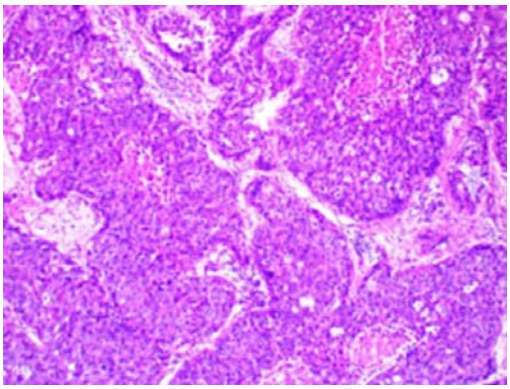

Fig. 2. Preoperative enhanced MRI image. The arrow indicated the tumor lesion
Source: Author

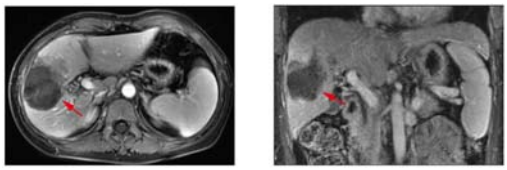

Fig. 3. Pathological diagnosis: (right half liver) hepatocellular carcinoma with moderate differentiation, (100×)
Source: Author

points, the Eastern Cooperative Oncology Group performance status (ECOG-PS) score was 1 point, the blood routine and coagulation function were normal, and the Model for End-Stage Liver Disease (MELD) score was 10 points. The indocyanine green retention test at 15 min (ICG-R15) for liver functional reserve was 8 percent. After multidisciplinary team (MDT) discussion, it was considered feasible to surgically resect the tumour.

Surgery was requested after the researchers communicated with the patient and her family, whom were informed of the risks and possible outcomes of the surgery and signed a written informed consent. On 20 November, 2020, the patient underwent right hepatectomy, cholecystectomy, portal vein incision and embolectomy and diaphragm repair. The postoperative pathological report showed that the area of tumour necrosis in the patient's right liver was about 60 percent, there was no cancer involvement in the liver tissue and the stump larger than 1 cm away from the mass, one '12p' lymph node was metastasised with no cancer, and the portal vein tumour thrombus was completely necrotic.

The patient had no significant postoperative complications and was discharged from the hospital on 1 December, 2020. She was readmitted on 12 April, 2021 for TACE intervention and continued to receive camrelizumab immunotherapy and apatinib targeted therapy every 3 weeks (250 mg/day).

Regular outpatient follow-up in the hospital after surgery showed that the level of tumour markers in this patient remained at a normal level (Table 1). The patient's latest upper abdominal MRI review was on 7 July, 2022, and still no signs of tumour recurrence were observed.

DISCUSSION

Surgery is regarded as the most essential radical treatment for solitary massive (≥10 cm) HCCs, since surgical treatment has a better survival probability than non-surgical treatment (Kokudo et al. 2016). However, HCC combined with PVTT has its potential problems, which is particularly significant in advanced liver cancer and portal vein tumour thrombosis, including intrahepatic spread, extrahepatic distant metastasis, postoperative recurrence, and poor overall prognosis of patients (Xu et al. 2019). In the present case, as the right-lobe tumour clung to the middle hepatic vein, the right hemi-hepatectomy was required to ensure a sufficient surgical margin, which may result in an increase in the rate of recurrence and metastasis is high after hepatectomy, and the presence of portal vein tumour thrombosis is also a high-risk factor for postoperative recurrence.

In recent years, as one of the most common treatment options for advanced liver cancer, preoperative TACE has emerged as a conventional available approach to lower the risk of postoperative morbidity and mortality in potentially resectable HCCs (Wang et al. 2021). TACE can block tumour blood supply and thereby lead to ischemia and hypoxia in embolized tissue cells and stimulate the vascular endothelial growth factor (VEGF) expression in residual lesions as well as to promote tumour angiogenesis. TACE combined with an anti-angiogenic drug can inhibit tumor blood vessel formation and create collateral circulation after TACE (Li et al. 2020). However, the efficacy and long-term prognosis of TACE on large HCC (≥10 cm) is limited, due to the decrease in response over repeated TACE treatment (Sieghart et al. 2015).

The BCLC staging system suggests that systemic therapy is the standard treatment for HCC of BCLC stage C (Reig et al. 2022). Some guidelines predominantly recommend TACE-based comprehensive therapy, comprising VEGFR-2 or PD-1 inhibitors. TACE and Apatinib have synergistic effects in treatment as Apatinib can reduce the incidence of tumour metastasis by inhibiting angiogenesis in tumour areas (Liang et al. 2019; Tian et al. 2011), while Camrelizumab injection, as a PD-1 inhibitor independently developed in China, has shown good efficacy and safety in a variety of malignant tumours (She 2020). Studies have shown that HCC patients who received preoperative TACE had higher PD-1 and PD-L1 expression in their tumour cells than HCC patients who did not receive preoperative TACE. Even though Camrelizumab is less effective in single-agent therapy for advanced liver cancer, it can effectively reduce the risk of increased PD-1 and PD-L1 after TACE monotherapy and thereby has an obvious synergistic effect with the TACE treatment (Montasser et al. 2021). Xu et al. (2019) reported that combining Camrelizumab injection with Apatinib for the treatment of patients with advanced liver cancer also has a synergistic effect and has shown a good therapeutic effect. TACE causes tumor tissue necrosis, releases tumor antigens, and enhances tumor-specific immune responses (Chang et al. 2019), and may transform an immunosuppressive microenvironment into immunosupportive and promote PD-L1 inhibitors response (Pinato et al. 2021). Further, anti-VEGF treatment can reverse VEGF-mediated immunosuppression and enhance anti-PD-1 or anti-PD-L1 efficacy (Hato et al. 2016; Deng et al. 2020). In the present case, the tumour volume and the level of tumour markers were significantly decreased after the application of TACE combined with Apatinib and Camrelizumab treatment and the patient was discharged from the hospital within 10 days. The adverse effects on liver function were manageable.

In the present case, the patient had a large tumour on admission that invaded the portal vein tumour thrombus and the right branch of the hepatic artery, and laparoscopic right hemi-hepatectomy was performed as the patient met the criteria for major hepatectomy. The main technical challenges during the operation were to ensure an adequate surgical margin and to prevent iatrogenic hematogenous spread of tumour cells. The re-

searchers used twice TACE and five times of carrelizumab immunotherapy to reduce the tumour size and tumour markers and win the chance of radical resection for patients. Surprisingly, in the process of the combination therapy, the patient had fewer drug-related adverse reactions, and the post-embolic syndrome was not obvious, which may be related to the patient's age advantage and individual tolerance. The patient had also received continued combination therapy for a long time after surgery. During repeated regular follow-up, the researchers found that the patient's disease-free survival rate and disease-free quality of life were impressive, which may contribute to the long-term survival of the patient.

CONCLUSION

This case demonstrates that TACE combined with Apatinib and Camrelizumab treatment appears to be both preoperatively and postoperatively safe and effective for BCLC stage C HCC. More multicentre prospective randomised clinical studies are required to validate the safety, feasibility, and efficacy of the approach.

RECOMMENDATIONS

TACE combined with Apatinib and Camrelizumab treatment appears to be safe and effective for BCLC stage C HCC both preoperative and postoperative, which may play a crucial role in the treatment of the HCC patients.

ABBREVIATIONS

HCC: hepatocellular carcinoma
PVTT: portal vein tumour thrombosis
TACE: transarterial chemoembolization
VEGFR-2: vascular endothelial growth factor receptor-2
IgG4: immunoglobulin G4
mAb: monoclonal antibody
NMPA: National Medical Products Administration
cHL: classical Hodgkin's Lymphoma
pCR: pathologic complete response
CT: computed tomography
AFP: alpha-fetoprotein
VEGF: vascular endothelial growth factor
BCLC: Barcelona Clinic Liver Cancer
ECOG-PS: Eastern Cooperative Oncology Group performance status
MELD: Model for End-Stage Liver Disease
ICG-R15: indocyanine green retention test at 15 min
MDT: multidisciplinary team

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Affiliated Hospital of North Sichuan Medical College, Institute of Hepatobiliary-Pancreatic-Intestinal of North Sichuan Medical College. Informed consent was obtained from all individuals included in this study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding authors.

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CONFLICTS OF INTEREST

There are no potential conflicts of interest to disclose.

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Not applicable.

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