Effective hepatic artery chemoembolization for advanced hepatocellular carcinoma with multiple tumor thrombi and pulmonary metastases: A case report

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Abstract. Advanced hepatocellular carcinoma (HCC) with tumor thrombi invading the portal vein and extending into the right atrium (RA) through the hepatic vein is regarded as a terminal-stage condition. Intracardiac tumor thrombus and treatment via liver resection has been reported in the current literature, but results from this therapeutic approach remain unsatisfactory. The present study describes a rare case of HCC with metastatic portal vein, middle hepatic vein, inferior vena cava (IVC) and RA tumor thrombi, and pulmonary metastases. A 29-year-old woman was admitted to The First Affiliated Hospital of Guangxi Traditional Chinese Medical University (Nanning, China) subsequent to experiencing right upper quadrant abdominal pain. Following diagnosis, based on computed tomography analysis and laboratory data, the patient underwent an initial transcatheter arterial chemoembolization (TACE) treatment using fluorouracil (5-FU), pirarubicin, mitomycin C, Lipiodol and sodium alginate microball (KMG). At 1 month post-treatment, serum α-fetoprotein levels remained at >1,000 ng/ml. Subsequently, the patient underwent a second TACE treatment. At 1 month after the second treatment, the abdominal pain had been alleviated and the serum α-fetoprotein levels were reduced to <20 ng/ml. Imaging analysis indicated a marked reduction in tumor burden in the liver and the hepatic vein and IVC tumor thrombi. Furthermore, the portal vein and RA tumor thrombi, and the pulmonary metastases had disappeared. At 40 months after the second TACE therapy, the patient remains alive without any signs of recurrence. The present case demonstrates that the administration of TACE, using 5-FU, pirarubicin, mitomycin C, Lipiodol and KMG, functions as an effective treatment in cases of unresectable advanced HCC presenting with pulmonary metastases and extensive tumor thrombi in the IVC, the RA and one branch of the portal vein.

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Introduction

Hepatocellular carcinoma (HCC) is the third highest cause of cancer-associated mortality worldwide following stomach and lung cancer (1). Liver cancer is the sixth most common cancer worldwide, accounting for 5.7% of all novel cancer cases. A total of ~82% of liver cancer cases occur in developing countries, with 55% occurring in China alone. There is a high incidence rate of HCC in Asia, and particularly so in China due to endemic hepatitis B and C (2,3). However, only <10% of patients in Asia and ~30% of patients in the West are eligible at diagnosis for potentially curative treatments, including resection or liver transplantation (4,5) and radiofrequency ablation (6,7).

Despite regular medical examinations, certain patients that are diagnosed with HCC also present with extensive tumor thrombi, typically extending into the inferior vena cava (IVC) and right atrium (RA) through the hepatic vein (8,9); this condition is considered as terminal-stage HCC. Intracardiac tumor thrombus and liver resection treatment have been reported in the current literature, alongside alternative therapeutic approaches (i.e., radiotherapy), but long-term results from such treatments remain unsatisfactory (10-15). Transcatheter arterial chemoembolization (TACE) has since been recommended for the treatment of these patients (16).

The present study describes the case of a patient with HCC and metastatic tumor thrombi of the right branch of the portal vein, inferior hepatic vein, IVC and RA, with pulmonary metastases. Following two effective TACE treatments, the patient remains alive at 40 months follow-up, without any signs of recurrence.

Case report

A 29-year-old woman with hepatitis B was referred to the First Affiliated Hospital of Guangxi Traditional Chinese Medical

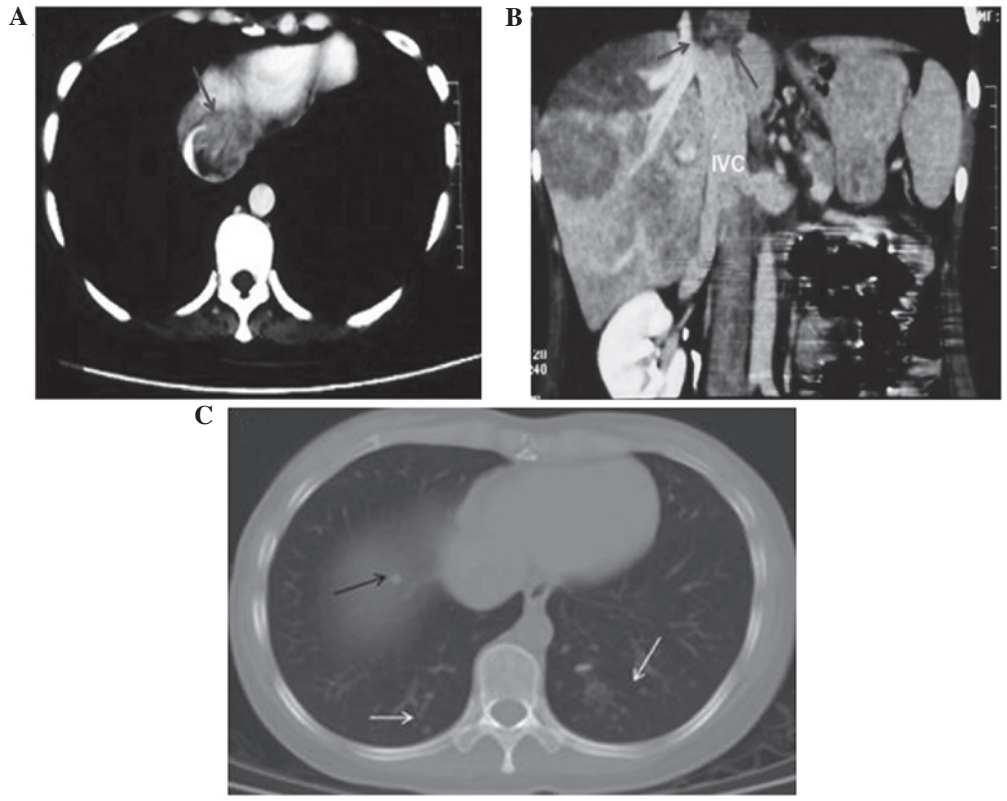

Figure 1. Abdominal CT prior to transcatheter arterial chemoembolization. Arterial phase of the CT scan, (A) cross-sectional scan and (B) coronal scan, presenting a well-defined, lobulated filling defect in the right atrium (arrows) and an irregular enhancement. (C) Chest CT scan exhibiting several solitary nodules (indicated by the black and white arrows) in the bilateral lower lobe lung, all of which were <0.5 cm in diameter. CT, computed tomography; IVC, inferior vena cava.

University (Nanning, China) on September 5, 2011, presenting with a 1-month history of right upper quadrant abdominal pain and abnormal shadows in the liver on an abdominal computed tomography (CT) scan (performed using a BrightSpeed Elite 16 slice CT scanner; GE Healthcare Life Sciences, Chalfont, UK) that had been performed prior to referral. Physical examination identified mild abdominal tenderness in the upper right quadrant, with no rebound tenderness. Cardiovascular, respiratory and neurological examinations were normal. The family history of the patient was non-contributory. Laboratory analysis provided the following results: Platelets, $201x10^9$/l (normal range, $100\text{-}300x10^9$/l); serum aspartate aminotransferase, 107 U/l (normal range, <40 U/l); alanine aminotransferase, 94 U/l (normal range, <40 U/l); total bilirubin, 9.1 μmol/l (normal range, <20 μmol/l); albumin, 31.7 g/l (normal range, 34-54 g/l); and prothrombin time, 14.5 sec (normal range, 12-14 sec). Screening for hepatitis B was positive for all antigens and negative for antibodies. The serum level of α-fetoprotein (AFP) was >1,000 ng/ml (normal range, <20 ng/ml). No abnormalities were observed on the electrocardiogram.

An abdominal enhanced CT scan was performed at the Guangxi Tumor Hospital (Nanning, China) hospital 4 days prior to admission, and revealed multifocal liver lesions of various sizes, ranging from 2.0-8.5 cm in diameter in segments 4, 5, 7 and 8, and a right portal vein tumor thrombus extending through the middle hepatic vein and IVC into the RA (Fig. 1A and B). A CT scan of the chest identified several solitary nodules in the bilateral lower lobes of the lungs, all of which were <0.5 cm in diameter (Fig. 1C). Echocardiography was not performed at that time, as the tumor thrombus could not be clearly observed on the CT scan.

A selective hepatic angiogram was performed during the first TACE treatment and revealed three large hypervascular areas in the right lobe of the liver supplied by the right hepatic artery (Fig. 2). These hypervascular areas were typical of HCC, and extended into the IVC and RA through the middle hepatic vein. The feeding arteries of the tumor thrombus and the tumor itself originated from the left and right hepatic arteries. Therefore, following imaging analysis, the patient was diagnosed with HCC complicated by portal vein, middle hepatic vein and metastatic right atrial tumor thrombi, with pulmonary metastases (no biopsy was performed to confirm the exact nature of these masses).

In September 2011, the patient underwent the first 6-week cycle of TACE treatment with fluorouracil (5-FU; 500 mg), pirarubicin (20 mg), mitomycin C (10 mg), super-liquid iodized oil (Lipiodol®; 9.5 ml; Guerbet, Aulnay-sous-Bois, France) and sodium alginate microball (KMG; 1.0 g; Beijing Shengyiyao Science & Technology Development Co., Ltd., Beijing, China). At 1 month after the initial TACE treatment, serum AFP levels remained at >1,000 ng/ml. No complications of TACE were observed, and the symptoms were partially relieved. CT revealed necrosis of a few of the tumor masses, but a number of active lesions remained. Therefore, in October 2011, the patient underwent a second 6-week cycle of TACE treatment with 5-FU (500 mg), pirarubicin (10 mg), mitomycin C (10 mg), super-liquid iodized oil (2 ml) and KMG (0.3 g).

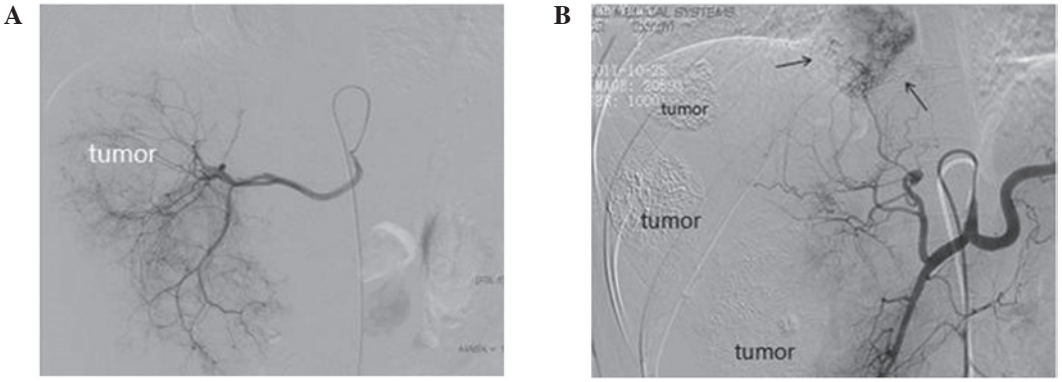

Figure 2. Angiographic image of the patient. (A) During the first TACE treatment, three large hypervascular areas of tumor staining were observed at the right liver lobe supplied by the right hepatic artery, which were typical of hepatocellular carcinoma. (B) The second TACE treatment revealed that the Lipiodol remained in the tumor of the right lobe liver. The tumor thrombus of the RA was a hypervascular lesion supplied by the right hepatic artery. The artery entered the RA by passing the inferior vena cava, and was of a 'grating'-like type (arrow). TACE, transcatheter arterial chemoembolization; RA, right atrium.

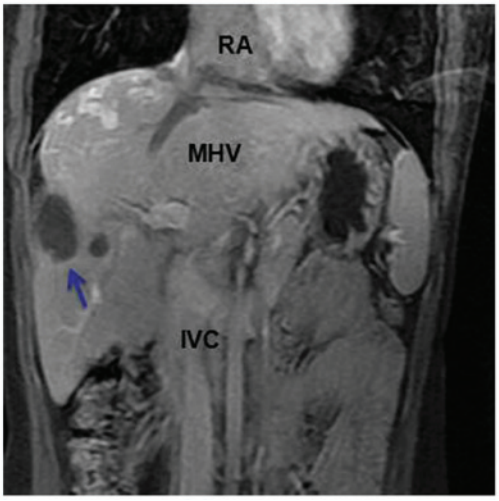

Figure 3. Magnetic resonance imaging demonstrating shrinkage of the right atrium tumor thrombus prior to its eventual disappearance. The liver tumors (arrow) and the tumor thrombus in the inferior vena cava and middle hepatic vein are also markedly reduced in size. RA, right atrium; MHV, middle hepatic vein; IVC, inferior vena cava.

At 1 month after the second TACE treatment, the right upper quadrant abdominal pain had disappeared. The serum AFP levels gradually decreased and fell within the normal range (<20 ng/ml). At a total of 4 months after the second TACE treatment, CT revealed that the lung metastases had disappeared. A magnetic resonance imaging (MRI) scan was performed (using a Signa HDxt 1.5T MRI scanner; GE Healthcare Life Sciences) 14 months after the second TACE treatment in order to detect any lesions that had been missed on the CT scan. MRI indicated that there was no active lesion, that the tumor thrombus in the right branch of the portal vein and RA had disappeared, and that the liver tumors and the tumor thrombus in the IVC and middle hepatic vein had markedly decreased in size (Fig. 3). Subsequent to therapy, the patient was not administered any further drug treatments, as the liver function remained normal. The patient has been regularly followed up, and at 40 months post-treatment is currently alive and well, exhibiting no signs of tumor progression and with excellent quality of life. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Traditional Chinese Medical University. Full informed consent was obtained from the patient.

Discussion

HCC is particularly prevalent in East Asia due to the high incidence of hepatitis B and C infection (2,3,17). Liver transplantation or hepatic resection is limited to a small number of HCC patients (18). Advanced HCC presenting with extensive intravascular tumor thrombi is a rare condition and is considered as a terminal stage of HCC (19-21). The majority of patients with terminal-stage HCC receive no anticancer treatment and typically succumb to the disease within a few months of diagnosis, with a median survival time of 2.0-3.5 months (11,22). The most appropriate treatment for patients with HCC metastases to the RA remains controversial (8-10,12,13,15,16,19,23). As the majority of patients are already in the advanced stage of the disease at diagnosis, aggressive treatment is not recommended. It was previously reported that the survival time following surgical removal of intra-atrial HCC ranged from 18 days to 56 months (median, 11 months), depending on the characteristics of each individual patient (23). However, regarding patients with HCC and tumor thrombi of the hepatic vein, portal vein and RA, plus pulmonary metastases, no effective therapy has yet been reported, with surgical resection being unsuitable for such patients. Alternative non-surgical therapies, including percutaneous ethanol injection, microwave coagulation therapy and irradiation, have also produced unsatisfactory results in patients with advanced HCC (5,11,21,24,25). Therefore, no standard regimens have yet been approved.

TACE has become the most successful treatment for advanced HCC, providing a survival benefit for selected patients (26). The treatment is extensively used in patients with HCC invading the portal vein, and also in those who are not suitable for surgery (27). Hepatic artery infusion chemotherapy is particularly effective in treating the disease and may offer survival benefits, even when the patient presents with extrahepatic metastases (28).

In the present study, TACE with 5-FU, pirarubicin, mitomycin C, Lipiodol and KMG achieved a marked anticancer effect, not only on the primary tumor, but also on the tumor

thrombi in the portal and hepatic veins and the RA, and on the pulmonary metastases. The patient is currently alive at 40 months post-treatment, which is far longer than the 2.0 to 3.5-month survival time typically observed in patients with this disease; however, it should be noted that the survival time of the patient is within the 18-day to 56-month range reported with the use of other treatment strategies. Emulsions of Lipiodol and chemotherapy have been reported to remain in the hepatic tissues for a long period of time after infusion through the portal vein and hepatic artery (29). The use of KMG induces permanent hepatic artery embolization and leads to long-term anticancer drug retention in the tumor.

A previous systematic review indicated that TACE improves the survival time of patients with unresectable HCC, and that it should be considered as a standard treatment (4). Another previous study in patients with HCC and thrombi of the IVC and RA treated with TACE reported that the median survival time in responders was 13.5 months (range, 1.5-79.7 months) compared with 3.3 months (range, 2.1-24.3 months) in non-responders (16). However, the tumor burden in these patients was less than that observed in the present case. Further trials should be conducted to assess the efficacy of TACE in such patients, however, the rarity of the disease would be a limiting factor on the number of trials that may be undertaken. Nevertheless, the few reported cases, including the present case, suggest that TACE may be an appropriate and successful approach to treat HCC patients presenting with multiple venous thrombi and distant metastases.

In conclusion, the current case may suggest that TACE, using 5-FU, pirarubicin, mitomycin C, Lipiodol and KMG, may serve as an effective treatment in patients presenting with unresectable advanced HCC with pulmonary metastases, and with extensive tumor thrombi in the IVC, the RA and one branch of the portal vein.

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