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Single Case

Diffuse Infiltrative Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis Completely Cured by Transcatheter Arterial Chemoembolization: Case Report with 8-Year Follow-Up

Suk Bae Kim

Department of Internal Medicine, Dankook University College of Medicine, Cheonan, South Korea

Keywords
Hepatocellular carcinoma · Portal vein tumor thrombosis · Transcatheter arterial chemoembolization

Abstract
Hepatocellular carcinoma (HCC) is the most common type of liver cancer and its treatment options are determined by shape, liver function, loci, and stages of cancer. Diffuse type of infiltrative HCC accompanied by portal vein tumor thrombosis (PVTT) has the poorest prognosis among other HCCs and there are no other prominent treatment options than systemic chemotherapy. In this study, we report a case of a 56-year-old man with diffuse infiltrative HCC accompanied by PVTT who achieved complete remission for 8 years after receiving conventional transcatheter arterial chemoembolization using adriamycin and gelfoam.

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Suk Bae Kim
Department of Internal Medicine
Dankook University College of Medicine
119 Dandae-ro, Dongnam-gu, Cheonan 31116 (South Korea)
E-Mail dryakson@hanmail.net

Introduction

Although hepatocellular carcinoma (HCC) is only the 6th most common cancer worldwide, it is very fatal, with the 3rd lowest survival rate among other types of cancers [1]. Especially the diffuse infiltrative type of HCC has a poorer prognosis than other types of HCC and, when accompanied by portal vein tumor thrombosis (PVTT), it leads to a dismal outcome, so we even recommend conservative treatments. Complete remission is very rare and unlikely in cases of HCC accompanied by PVTT, or diffuse-type HCC. However, two exceptional cases leading to complete remission have been reported. One case involved HCC accompanied by PVTT treated with sorafenib [2], and the other case was diffuse HCC treated with transcatheter arterial chemoembolization (TACE) [3]. Herein, we report a case of diffuse infiltrative HCC accompanied by PVTT showing complete remission after TACE was performed twice, with no recurrence after more than 8 years of close monitoring.

Case Presentation

A 56-year-old male visited our hospital in January 2008. He had been previously found to have liver tumors using dynamic liver computed tomography (CT). One tumor was located in segments 4 and 8. It measured 11.3 × 9.0 × 7.8 cm, was enhanced weakly and heterogeneously during the arterial phase, was washed out during the delayed phase, and had no clear boundary (Fig. 1a). Several other tumors were present in segments 7 and 8. They had similar shapes and were 1~2 cm in length. A 1.5-cm thrombosis was found in the left portal vein, while right portal vein thrombosis was found throughout the whole right portal area, starting at the origin of the portal vein (Fig. 1b). The patient had been diagnosed in our hospital in 1994 with chronic hepatitis B and liver cirrhosis, but was not receiving regular examinations or treatments.

Blood test conducted after hospitalization revealed a platelet count of 144,000/mm^3, aspartate aminotransferase of 51 U/L, alanine aminotransferase of 53 U/L, total bilirubin of 0.71 mg/dL, albumin of 4.3 g/dL, and prothrombin time of 11.7 s (INR 0.97). Tumor marker test revealed α-fetoprotein (AFP) of 61,042 ng/mL and des-γ carboxyprothrombin of 23,000 mAU/mL. Surgical treatment was not available due to the heavy portal vein invasion and massive diffuse infiltrative HCC. Accordingly, TACE was performed.

Outcome of TACE showed existence of a huge tumor staining in segments 4 and 8, along with the staining of right PVTT. A mixture (total 18 mL) of adriamycin 50 mg and lipiodol 15 mL was administered (Fig. 2). Dynamic liver CT scan taken after about a month showed large and heterogeneous lipiodol uptake mainly at segments 4 and 8 (Fig. 3a). The left and the right PVTT were still found, although they were reduced in size. Another small partial lipiodol uptake was found in segments 7 and 8. Blood testing revealed reduced AFP and des-γ carboxyprothrombin levels (5,685 ng/mL and 162 mAU/mL, respectively).

The second TACE was conducted in February 2008. A weak tumor staining in segment 8 was found, so a mixture (total 7.4 mL) of adriamycin 50 mg and lipiodol 10 mL was administered to the patient. No tumor staining was found in the PVTT. When the dynamic liver CT scan was taken 2 months later and compared to the previous CT scan, no increase in lipiodol uptake was evident. Blood test revealed normalized AFP and des-γ carboxyprothrombin (2.73 ng/mL and 19 mAU/mL, respectively). The patient then underwent follow-up monitoring with dynamic liver CT and tumor marker levels every 3~4 months. Follow-up results showed that the lipiodol uptake and PVTT had completely disappeared with no residuals

(Fig. 3b, c). The latest tumor marker assay revealed an AFP of 1.5 ng/mL and a des-γ carboxyprothrombin of 12 mAU/mL. The patient has not shown any signs of recurrence for the past 8 years.

Discussion

HCC can be classified into nodular, massive, and diffuse types according to their shapes. Among them, the diffuse type, which comprises 7~13% of all HCC, carries the poorest prognosis [4, 5]. Infiltrative HCC is a subtype of the diffuse type; it has an especially poor prognosis because it is often advanced upon diagnosis and is impossible to treat with surgical operations or locoregional treatments like radiofrequency ablation. Thus, patients with infiltrative type of HCC receive intra-arterial therapy (IAT), such as drug-eluting beads TACE, conventional TACE, and yttrium-90 or systemic chemotherapy like sorafenib.

IAT for infiltrative HCC can increase the median survival rate compared to the supportive care (12 vs. 3 months), but its outcome is still poorer compared to other types of HCC [6]. One analysis conducted in Korea with 35 diffuse infiltrative HCC patients reported that TACE treatment increased survival of patients with good liver function [7]. In the present case, the patient would have received IAT considering his good Eastern Cooperative Oncology Group (ECOG) status and liver function, although he had diffuse infiltrative HCC and malignant tumor thrombosis in the portal vein.

The average survival period for infiltrative HCC patients is approximately 10 months, with AFP level and liver function correlated with the prognosis. Especially if bilirubin exceeds 2 mg/dL and AFP exceeds 400 ng/mL, the prognosis is not good [6]. Concerning sorafenib treatment for infiltrative HCC, even though the overall survival time increased from 7.9 to 10.7 months, median time to symptomatic progression showed no significant difference in other studies (4.1 compared to 4.9 months), indicating that sorafenib is less effective than IAT [8].

What is peculiar for this patient was that he had shown complete remission for more than 8 years without any recurrence, even though he also had PVTT. Malignant portal vein thrombosis is the critical factor among other risk factors leading to poor prognosis. Vascular endothelial growth factor has an important role in the occurrence of PVTT [9]. Identifying the malignant thrombosis from bland thrombosis is important. If the contrast is enhanced in the angiography (as was shown in this case) and if high fluorodeoxyglucose uptake is found on positron emission tomography-CT, malignant thrombosis can be diagnosed.

PVTT occurs in up to 30% of HCC patients, resulting in very short median survival periods (range, 2.7~4 months) [10]. Thus, European Association for the Study of the Liver guidelines classify PVTT as the advanced stage and recommend conservative treatment. But, since TACE is reported to be safe and effective for patients with HCC accompanied by PVTT, TACE has been performed for patients with relatively good liver function. TACE treatment produces varied results, with an overall response rate of 17~61.9% [11–13]. If accompanied by PVTT, the median survival time can vary depending on the type of HCC, with reported rates of 8.1 months for the segmental type and 4.3 months for the major type (first-order branch or main trunk) [14]. Our case was a major type with tumor thrombosis all through the right portal vein.

Tumor size influences survival; tumors exceeding 11.1 cm have a reported median survival period of 4.4 months, with 5.8 months for smaller sizes. The number of tumors is also influential, with a survival of 4.4 months for ≥2 tumors and 6.2 months for fewer tumors

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[14]. In the current case, the tumors exceeded 11.1 cm and there were more than 2, so the initial prognosis was expected to be bad. In addition, although sorafenib is reportedly effective on PVTT due to inhibition of vascular endothelial growth factor receptor and administration of sorafenib to HCC patients has been effective for the removal of PVTT [2], there has not been a report of the success of conventional TACE in complete removal of PVTT and HCC cure.

TACE is effective in downstaging, enabling 8~18% salvage surgical resection for patients with unresectable HCC, leading to an increased survival rate of 24.9~57% [15]. In this case, after TACE was performed, the malignant tumor thrombosis disappeared, lipiodol uptake gradually decreased, and resectability increased, which made surgery a viable option. But, as there is no sufficient data for this particular situation, it was hard to make a decision for the surgery. For this case, the authors will continue monitoring the patient as the lipiodol uptake has disappeared and there is no evidence of recurrence.

Conclusion

According to the Barcelona Clinic Liver Cancer staging, diffuse infiltrative HCC accompanied by PVTT is in category C, an advanced stage, where use of sorafenib is usually recommended. Although this 56-year-old male patient should have been administered sorafenib as he was in the advanced stage, it was not available at that time in Korea. Due to the patient's relatively good liver function and promising ECOG performance, the author conducted the TACE and a positive outcome has been evident for 8 years. In case of portal vein invasion, the classification changes from intermediate stage to advanced stage. As in this case, we found that the PVTT can be cured completely with TACE, which encourages us to recommend TACE for patients with good liver function, even with an advanced-stage disease.

Statement of Ethics

The author has no ethical conflicts to disclose.

Disclosure Statement

The author declares no conflict of interest.

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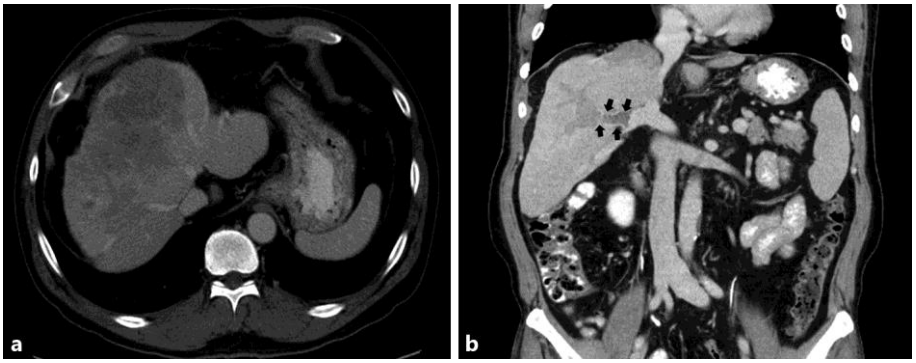

Fig. 1. Dynamic liver computed tomography. **a** Low-density lesions without definite margin of massive infiltrating HCC involving segments 4 and 8 (11.3 × 9.0 × 7.8 cm) on the portal phase. Other small similarly patterned lesions were found on segments 7 and 8. **b** Total occlusion of the right portal vein by malignant tumor thrombosis (black arrows) was found on the coronary section.

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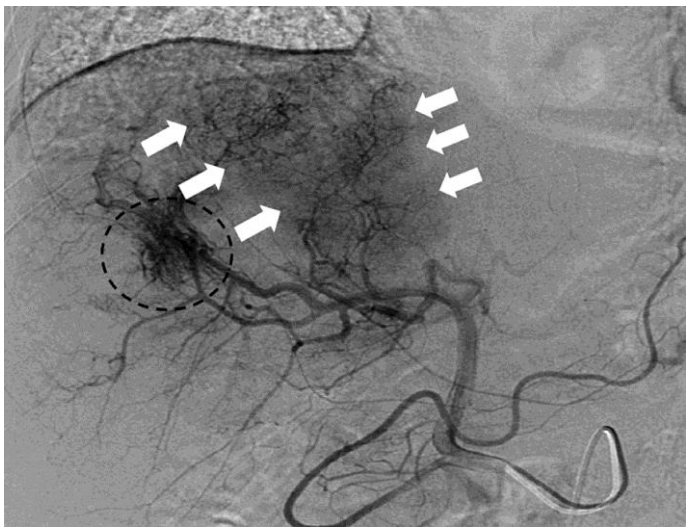

Fig. 2. Transcatheter arterial chemoembolization. Large tumor staining (white arrows) and portal vein tumor thrombosis staining (dotted circle) was found. A total of 18 mL mixture of adriamycin 50 mg and lipiodol 15 mL was infused and embolization using gelfoam was done.

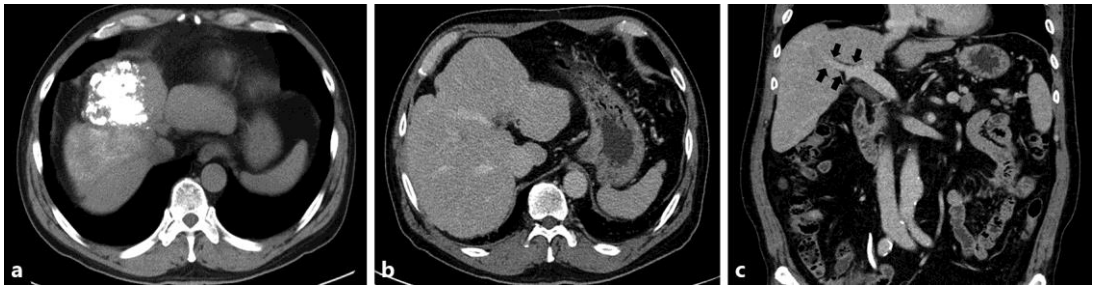

Fig. 3. Serial changes of dynamic liver computed tomography (CT). **a** CT after first transcatheter arterial chemoembolization. Irregularly margined and relatively good lipiodolization of diffuse infiltrating HCC involving segments 4 and 8 was noted. **b**, **c** Dynamic liver CT after 8 years. **b** Lipiodolization completely disappeared on recent CT. **c** Previous malignant tumor thrombosis of right portal vein clearly disappeared and now the portal vein is patent (black arrows).