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Case Report

A Case of Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis Successfully Treated by a Combination of Intra-Arterial Infusion 5-Fluorouracil, Cisplatin, and Systemic Interferon-α Therapies

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A 58-year-old female with hepatitis C was referred to our hospital after computed tomography (CT) revealed a tumor in the right lobe of her liver. After thorough examination, tumor thrombosis was detected on the main trunk of the portal vein, and we decided to administer a combination of subcutaneous interferon-alfa and intra-arterial 5-fluorouracil. However, after 2 cycles of treatment, this regimen was ineffective, and thus cisplatin (CDDP) was added for the third cycle. On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography. Hence, chemotherapy was considered effective and stopped. Two years after chemotherapy, Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonists-II (PIVKA-II) levels were within normal limits. Combination therapies have been recognized recently, and judging from the above case, the addition of CDDP to the combination regimen can prove beneficial.

Key words: Hepatocellular carcinoma – Portal vein tumor thrombosis – INF-α – Intra-arterial chemotherapy

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There is no effective treatment for cases of hepatocellular carcinoma (HCC) with main portal vein tumor thrombosis (PVTT). Moreover, the prognosis of inoperable cases is extremely poor, and some authors have reported that the average life span after diagnosis is 3 to 6 months. Recently, however, a combination of systemic interferon-alfa (INF-α) and intra-arterial 5-fluorouracil (FU) has been reported to improve the prognosis of the disease. Furthermore, partial and complete response cases are reported to achieve high survival rates of 100% at 1 year and 80% at 3 years. The interaction between INF-α and 5-FU promotes apoptosis and suppresses cell proliferation and angiogenesis and is therefore being considered a standard treatment option for HCC with PVTT. If the treatment is not effective, the patient can be administered additional medication. In this case study, it was seen that systemic INF-α therapy and intra-arterial infusion of 5-FU in combination with cisplatin (CDDP) were effective for both recovery and long-term survival of a patient with HCC and PVTT.

Case report

A 58-year-old female was referred to the outpatient clinic of our hospital after computed tomography (CT) revealed a tumor in the right lobe of her liver. The patient was infected with hepatitis C virus (HCV) by blood transfusion 35 years ago, but she did not receive treatment and visited our hospital for a thorough examination and treatment. Clinical tests on admission indicated abnormal liver function, and laboratory data showed abnormally high levels of aspirate aminotransferase (AST; 166 IU/L) and alanine aminotransferase (ALT; 188 IU/L). The levels of total bilirubin were normal (0.8 mg/dL). The prothrombin time was 82%, and the indocyanine green retention rate at 15 minutes was 36.8%. The levels of tumor markers AFP and PIVKA were found to be elevated at 48.2 ng/mL and 19,362 U/mL, respectively, indicating advanced HCC. Liver cirrhosis was defined as grade A according to Child's classification. CT and abdominal angiography revealed PVTT, which was then treated by INF-α and intra-arterial 5-FU combination chemotherapy. Hepatectomy and embolization therapy were contraindicated in this case. Pretreatment images are shown in Fig. 1. CT arterial portography and CT hepatic arteriography revealed that the tumor was in the right lobe of her liver and had infiltrated the main trunk via the first branch of the portal vein. Arterial portography using contrast medium revealed a flow defect at the main trunk of the portal vein. ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) revealed abnormal uptake in the right lobe of her liver (maximum standardized uptake value, 3.0; Fig. 1). The protocol of this combination therapy was as follows: 5-FU 500 mg/d (days 1–7, weeks 1–2), INF-α 5 million units (days 1, 3, and 5; weeks 1–4). However, after 2 cycles of treatment, this regimen was ineffective, thus CDDP was added for the third cycle. On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or FDG-PET (Fig. 2). Hence, chemotherapy was considered effective and stopped. A combination therapy of INF-α and revabirin was started to combat hepatitis C. Two years after chemotherapy, AFP and PIVKA-II levels were within normal limits. However, 3 years and 6 months after chemotherapy, a new lesion was detected in the left lobe of the liver on CT scan, along with increased HCV titers; and the lesion was treated by radiofrequency ablation (RFA). New lesions were detected in the right lobe of the liver after 1 year and after 2 years of RFA treatment, and were treated by transcatheter arterial embolization (TAE) therapy. After treatment with TAE, no lesion was detected, and the patient achieved a 5-year survival. Changes in tumor marker levels and HCV titers are shown in Fig. 3.

Discussion

The incidence of HCC, one of the most common cancers, has been on the rise in Japan for the past 30 years.[1] Recent developments in imaging techniques have made it possible to detect even a small lesion at an early stage. Although prognosis of total HCC has improved, that of advanced cases with PVTT continues to be poor. Numerous therapies have been implemented to treat advanced cases with PVTT, but none have been effective. The prognosis of inoperable cases that have been reported is estimated to be extremely poor, with an average life span of only 3 to 6 months after diagnosis.[2,3] Recently, a combination of intra-arterial 5-FU and systemic INF-α was reported to be more effective than treatment with arterial 5-FU alone for inoperable cases, resulting in an improved prognosis compared with operable cases.[4–6] Obi reported that the complete response cases of HCC with PVTT, which constitute 15%, showed a 1-year survival rate of over 80%.[4] The interaction between INF-α and 5-FU promotes apoptosis and suppresses cell proliferation and angiogenesis.[7,8] Prognosis of high-expression

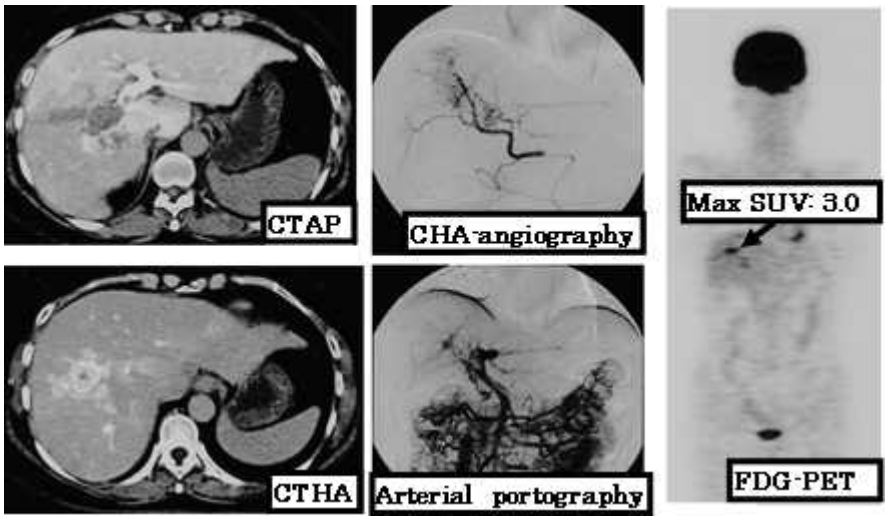

Fig. 1 CT arterial portography and CT hepatic arteriography reveal a tumor, in the right lobe of the liver, that infiltrated the main trunk via the first branch of the portal vein. Arterial portography using contrast medium reveals a flow defect at the main trunk of the portal vein. FDG-PET reveals abnormal uptake in the right lobe of the liver (maximum standardized uptake value, 3.0).

groups of type-I interferon receptor is reported to be better than that of low-expression groups for gastrointestinal cancer; however, the function of this receptor in HCC has not been identified.[7,8] In our case, the above-mentioned combination therapy was only slightly effective and complete response was achieved with the addition of CDDP. Addition of other chemotherapy drugs is considered to be effective in cases that do not respond to standard combination therapy. The recent developments in radiation techniques have enabled the use of local radiation therapy. Radiation-induced hepatitis usually occurs after whole liver irradiation to total 30 Gy; however, three-dimensional conformal radiation therapy (3DCRT) for PVTT has been reported to be effective, even with high focal doses (60 Gy), without causing any damage to the normal liver parenchyma tissue.[9–11] Some studies conducted on TAE and 3DCRT have reported significantly high survival rates in the responders compared with the nonresponders, while others have reported no difference in survival rates between the 2 groups.[10,11] The drawback of this TAE-3DCRT combination therapy was that the therapy failed to suppress intrahepatic metastasis.[10] Large-scale studies of 3DCRT and arterial chemotherapy have not yet been conducted, thus making the findings of our study on combination therapy valuable. We experienced one case of HCC with PVTT that showed complete recovery with local radiation therapy for PVTT and intra-arterial 5-FU infusion. The patient is currently alive having survived for

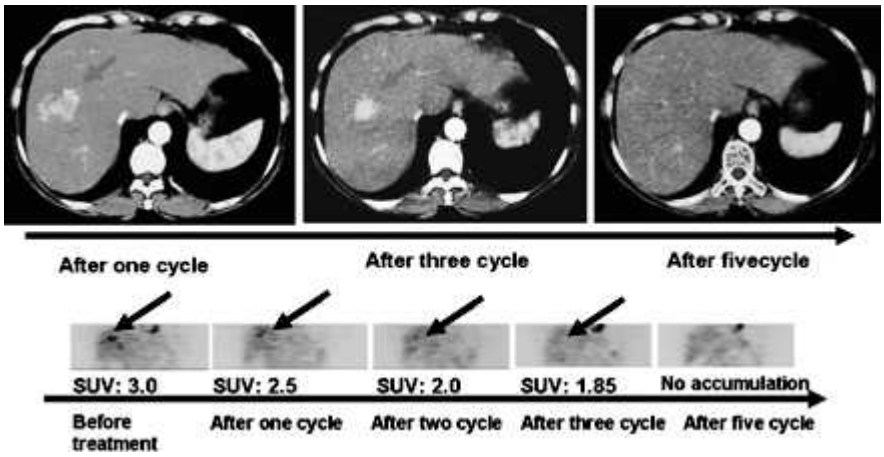

Fig. 2 On completion of 5 treatment cycles, the tumor and portal vein tumor thrombosis were not detected by CT or FDG-PET.

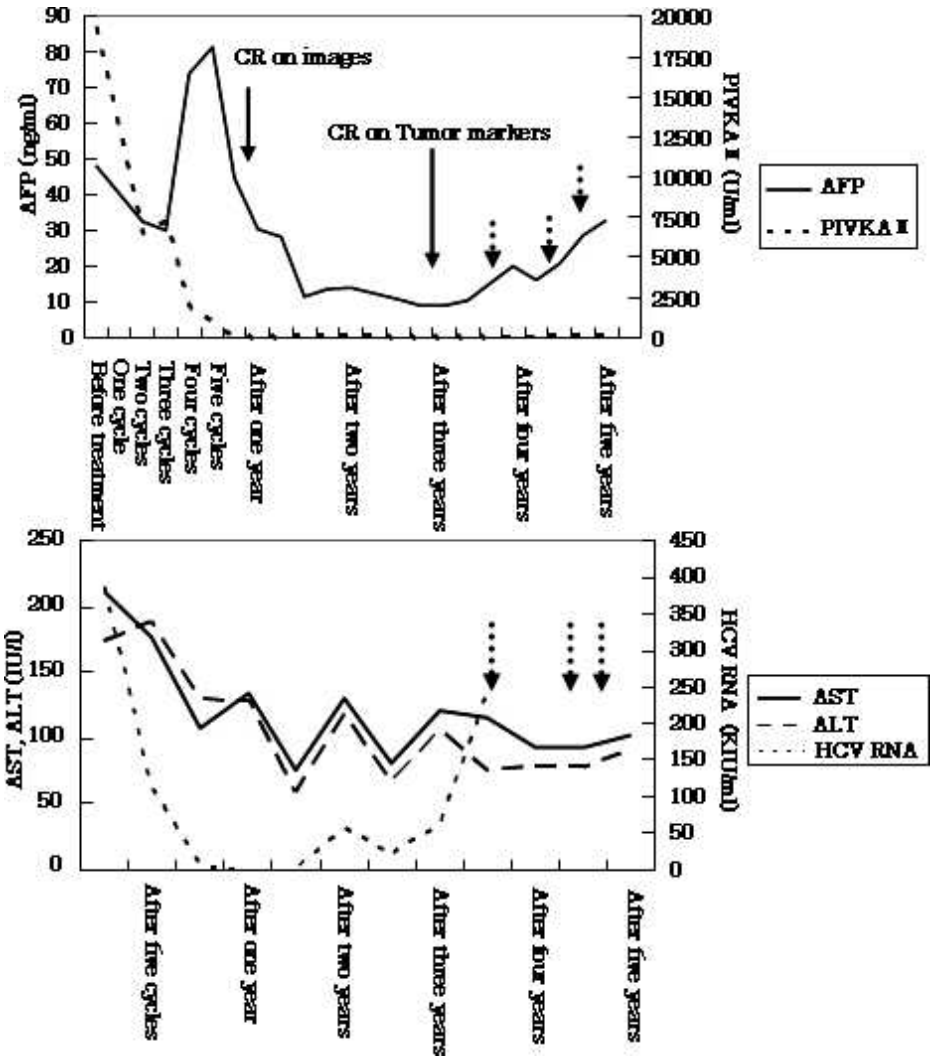

Fig. 3 The top graph shows changes in tumor markers. The bottom graph shows AST, ALT and HCV titers. The broken arrow indicates a period of recurrence.

over 5 years without recurrence. We might include local radiation in the treatment regimen for similar/future cases. In the future, a combination of local radiation therapy along with INF-α, intra-arterial 5-FU, and other carcinostatic drugs should be considered as the basic protocol for HCC with PVTT.

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