

Elevated α -Fetoprotein in the Absence of Carcinoma Caused by Relapse of Hepatitis C Viral Infection after Liver Transplantation

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ABSTRACT

We report a rare case of marked elevation of α -fetoprotein in the absence of hepatocellular carcinoma caused by a relapse of hepatitis C virus (HCV) infection. A 58-year-old man underwent liver transplantation to treat hepatocellular carcinoma caused by HCV-related liver cirrhosis. The HCV was of genotype 2a, and the ribonucleic acid titer was >8.0 log IU/mL. Direct-acting antiviral drugs were prescribed for 12 weeks; however, the HCV infection relapsed after treatment had ended, and α -fetoprotein levels increased to 8,981 ng/mL. Imaging did not reveal any malignancies. The patient initiated interferon therapy, at which time AFP levels decreased, and the HCV was successfully cleared.

INTRODUCTION

Hepatitis C virus (HCV) infection frequently recurs in liver transplant (LT) recipients with hepatocellular carcinomas (HCCs) caused by HCV-related liver cirrhosis.¹ HCV re-infection triggers inflammation of the host liver.² The level of α -fetoprotein (AFP) is a diagnostic marker of HCC, although the proportion of lecitine (L3) is more specific. AFP levels also increase during viral hepatitis.² The recurrence-free survival rate has been reported to be 83% after LT in patients who had undergone LT due to HCC.³

CASE REPORT

A 58-year-old Asian man underwent LT to treat HCC caused by HCV-related liver cirrhosis. He had no history of treatment for HCV prior to transplant. One HCC (5.0 cm in diameter) was located in S5 and was moderately differentiated and of the simple nodular type; another HCC (1.5 cm in diameter) was located in S8/4 and was of the green hepatoma type (ie, associated with mutations in the hepatocyte nuclear factor 1A gene). No portal invasion was apparent. The patient's AFP level was 153 ng/mL.

After LT, HCV of genotype 2a re-infected the grafted liver. The HCV ribonucleic acid (RNA) level was >8.0 log IU/mL. We started the patient on an immunosuppressant cocktail of tacrolimus, mycophenolate mofetil, and a steroid (methylprednisolone/prednisolone) (Figure 1). Transaminase and total bilirubin levels increased 2 months after LT, and fibrosing cholestatic hepatitis was suspected. Therefore, direct-acting antiviral drugs (ie, sofosbuvir+ribavirin 400 mg once daily) were given for 12 weeks. The HCV RNA level fell during treatment but increased again 1 month later, in association with marked elevation of liver enzymes. The steroid and mycophenolate mofetil were discontinued, and a daily injection of glycyrrhizin (SNMC; 80 mL stronger neo-minophagen C containing 40 mg glycyrrhizin in 20 mL) was commenced. At 6 months post-transplant, although the transaminase levels had

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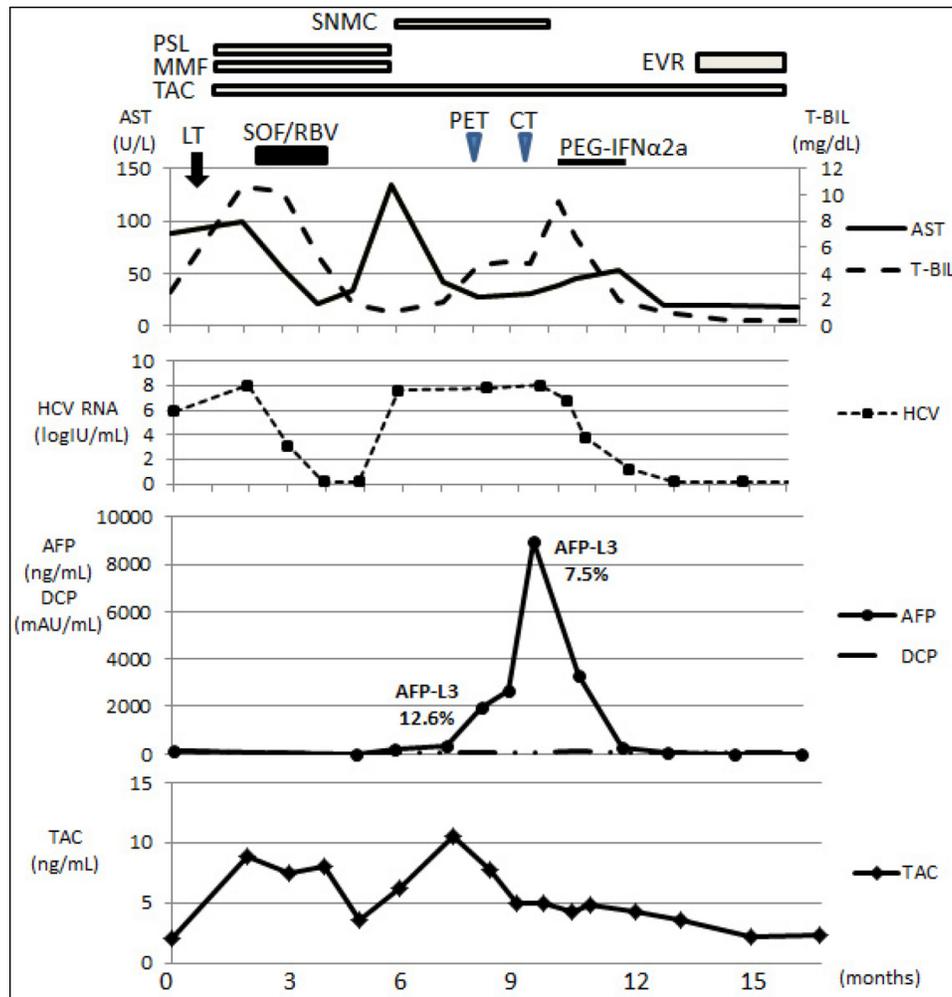


Figure 1. The α -fetoprotein level was notably elevated in the absence of hepatocellular carcinoma at 9 months post-liver transplant, and the level normalized after interferon therapy. PSL, methylprednisolone/prednisolone; MMF, mycophenolate mofetil; TAC, tacrolimus; SNMC, stronger neo-minophagen C; EVR, everolimus; LT, liver transplantation; SOF, sofosbuvir; RBV, ribavirin; PET, positron emission tomography; CT, computed tomography; PEG-IFN, pegylated-interferon; AST, aspartate aminotransferase; T-BIL, total bilirubin; HCV, hepatitis C virus; AFP, α -fetoprotein; DCP, des-gamma-carboxy prothrombin; HCC, hepatocellular carcinoma.

improved, AFP levels were elevated to 167 ng/mL. Blood testing revealed aspartate aminotransferase 134 U/L, alanine aminotransferase 147 U/L, HCV RNA 7.6 log IU/mL, and des-gamma-carboxy prothrombin (DCP) 47 mAU/mL. Although we searched for HCC via whole-body imaging (including the brain, lungs, abdomen, and pelvic cavity), all results were negative, and an ascites aspirate assay revealed no malignant cells. Fluorodeoxyglucose-positron emission tomography and computed tomography scans from head to pelvis/prostate were performed at 8 months post-transplant (Figure 2). No HCC or AFP-producing tumor was detected. AFP levels increased to 8,981 ng/mL (L3 proportion, 7.5%) at 9 months; DCP levels were 74 mAU/mL at this time. A once-weekly pegylated interferon (IFN)- α -2a treatment was commenced to prevent HCC development. Fever and pancytopenia developed, and treatment was stopped 6 weeks later. The

condition improved on discontinuation of IFN. In addition, HCV RNA levels fell, and a sustained virological response was obtained. AFP levels gradually decreased to undetectable levels by 17 months post-transplant.

DISCUSSION

AFP is a glycoprotein secreted by fetal cells during embryogenesis and is a well-known diagnostic marker of HCC.² However, the sensitivity and specificity of AFP in terms of HCC detection are only 41-65% and 80-90%, respectively.^{4,5} AFP is also elevated in various extrahepatic tumors, including gastrointestinal tract tumors and pancreatic, gallbladder, lung, and bladder cancers.⁶ AFP levels >1,000 ng/mL are highly indicative of HCC. AFP-L3 exhibits the highest lectin affinity and is commonly seen in patients with HCCs. Some

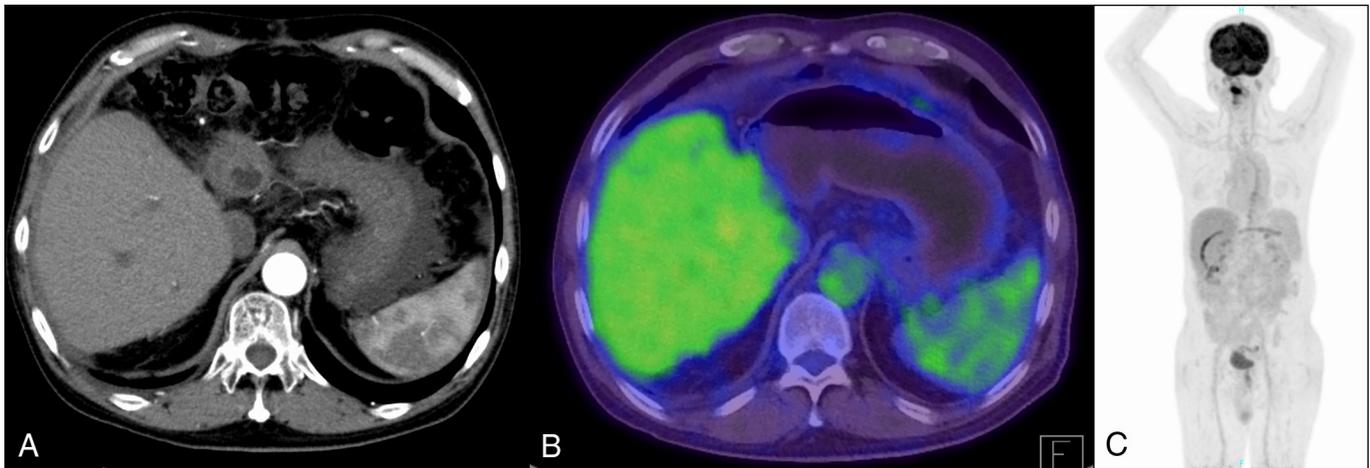


Figure 2. Post-liver transplant images: (A) Abdominal computed tomography. (B) Fluorodeoxyglucose-PET (FDG-PET) and CT scans of the liver. (C) FDG-PET and CT scan of the whole body 8 months after transplant. No malignancy was apparent.

reports have described AFP elevation in the absence of HCC; however, in these cases the AFP levels were only around 2,000 ng/mL.⁷⁻¹⁰ Viral infections activate multiple proinflammatory mediators such as tumor necrosis factor α , malondialdehyde, and nitric oxide, which recruit immune cells to the liver to generate an antiviral response.¹¹ It is believed that AFP elevation is attributable to hepatic inflammation and viral replication. Elevated levels of AFP as high as 5,480 ng/mL that resulted from chronic viral hepatitis have been described, as well as a reduction in levels with both IFN and direct-acting antiviral drug therapy; in addition, the measurement of the L3 proportion is important to diagnose HCC.^{12,13}

In our patient, his AFP levels increased to 8,981 ng/mL without an increase in the proportion of L3. DCP, which perhaps is best known as the protein induced by vitamin K deficiency or antagonist II (PIVKA-II) and as an abnormal form of prothrombin, is another biomarker of HCC, and it was not significantly increased in this case.¹⁴ We found no evidence of HCC or an AFP-producing tumor, and we doubt that an occult cancer was present. Direct-acting antiviral drugs often exhibit high efficacy and tolerability in patients after LT, but they cannot be administered to patients with HCCs.¹⁵ Thus, we selected IFN therapy because of its association with reduced HCCs.^{16,17} AFP levels decreased after the eradication of HCV. There is some risk of AFP increase associated with chronic hepatitis, and elevated AFP serum levels, elevated aspartate aminotransferase, prolonged international normalized ratio (international normalized ratio), hepatic steatosis, and HCV load are significantly associated with fibrosis.¹⁸ In our case, we speculate that acute HCV overgrowth due to immunosuppression in this LT recipient may contribute to a strong host-immune response and accelerated liver inflammation, leading to a sharp increase in AFP. Although the HCV RNA viral load was high, the AFP elevation occurred at 9

months post-transplant despite the decreased aspartate aminotransferase level after treatment with SNMC, which has been shown to have an anti-inflammatory effect and is approved in Japan for the treatment of chronic hepatic diseases.¹⁹ In patients who do not tolerate anti-viral therapy for HCV, ursodeoxycholic acid and/or glycyrrhizin is selected to reduce the transaminase level. In addition, it may be assumed that the rise in AFP levels was due to liver regeneration; however, the underlying mechanism is unknown.

We present a rare case with AFP elevation above 8,000 ng/mL attributable to acute hepatitis exacerbation in the absence of HCC under immunosuppressive conditions. The condition normalized following anti-viral therapy. In cases exhibiting AFP elevation, malignancy should first be ruled out, and thereafter viral inflammation should be considered as a potential cause.

DISCLOSURES

Author contributions: T. Kogiso wrote the manuscript, T. Sagawa collected the data, Y. Kotera performed the liver transplant, H. Egawa provided advice regarding this case report, and M. Yamamoto and K. Tokushige supervised this case study. K. Tokushige is article guarantor.

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Informed consent was obtained for this case report.

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