

# Acute Exacerbation of Hepatitis in Liver Cirrhosis with Very High Levels of alpha-Fetoprotein But No Occurrence of Hepatocellular Carcinoma

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Aminotransferase levels do not always increase during acute hepatitis or during an acute flare-up of chronic hepatitis. Persistently increased levels of serum alpha-Fetoprotein in an adult with liver disease suggest not only the presence or progression of hepatocellular carcinoma or its recurrence after hepatic resection or after other therapeutic approaches such as chemotherapy or chemoembolization, but also it suggests that there is an acute exacerbation of hepatitis or liver cirrhosis. We report here on two unusual cases of HBV- & HCV-related liver cirrhosis with acute exacerbation of hepatitis in which there was an insignificant elevation of the aminotransferase levels, but there were markedly increased alpha-Fetoprotein levels observed. The levels of alpha-Fetoprotein decreased gradually in both cases since the beginning of antiviral therapy, which implies that the increased levels were due to aggravation of the accompanying hepatitis. These cases also emphasize that using only the measurement of alpha-Fetoprotein is not sufficient for the diagnosis of hepatocellular carcinoma, and that this diagnosis also requires a more specific measurement such as AFP L3 along with the standard imaging studies.

**Key Words :** Alpha-Fetoprotein (AFP), Hepatocellular carcinoma, Hepatitis, Liver cirrhosis

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## INTRODUCTION

Acutely increased levels of aminotransferases will lead the physician to strongly suspect the presence of acute hepatitis or an acute exacerbation of chronic hepatitis. However, this does not correlate well with the degree of liver cell damage, and an alpha-Fetoprotein (AFP) level greater than 500 ng/mL is considered to be specific for the occurrence of hepatocellular carcinoma. We report here on our experiences with two rare cases of acute flare-ups of hepatitis B and C in patients with liver cirrhosis that accompanied minimal change in the levels of aminotransferases, but there was a markedly increased AFP level of over 4,000 ng/mL in each case, which prompted a

vigorous search for hepatocellular carcinoma. No definite evidence of a tumor could be identified, but in both cases the AFP levels decreased in response to antiviral therapy.

## CASE REPORT

### Case 1

A 59-year-old male with confirmed hepatitis C-related liver cirrhosis of over 10 years duration was admitted to our hospital in March 2003 for an evaluation of his functional and histopathologic status of the liver, and his levels of aminotransferases and alpha-Fetoprotein (AFP) that were checked at

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**Table 1.** Aminotransferases and alpha-Fetoprotein levels in the hepatitis C patient with liver cirrhosis

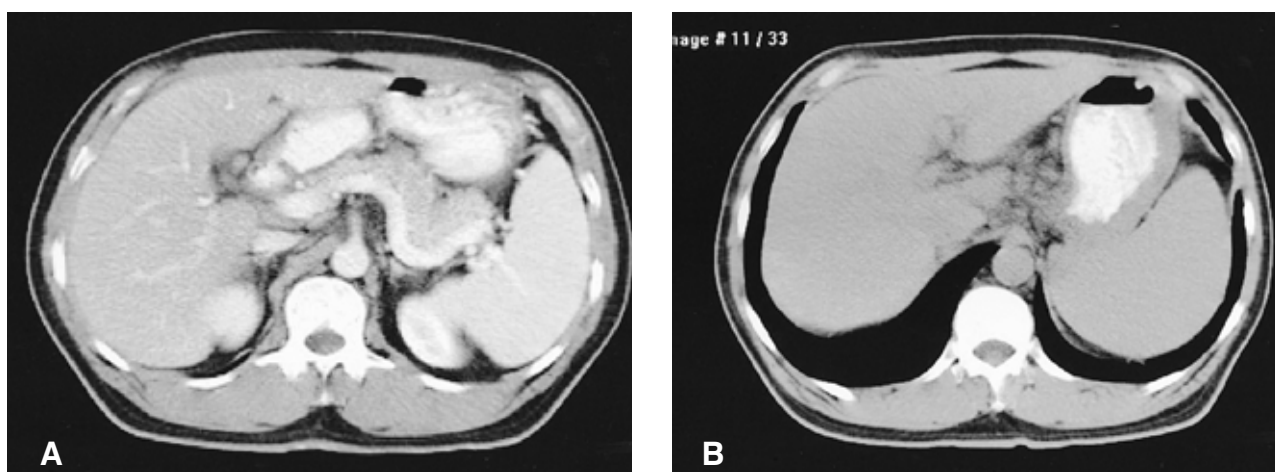
Year	2002'					2003'									
	Month/Day	5/11	9/19	10/14	11/13	12/30	2/19	3/5	3/12	3/26	4/8	6/11	8/11	9/19	11/21
AST/ALT	57/18	137/43	129/45	174/80	173/66	196/71	185/34			85/76	73/74	89/90	59/72	87/74	96/59
T-BIL	0.9	1.0					1.3			0.9	0.9	0.8	1.1	0.8	
PT	1.21	1.28					1.42		1.33	1.35	1.32	1.33	1.25	1.35	
PLT	131K	98K					105K		82K	72K	66K	90k	85k	80k	
AFP	18.1	99.5	75.5	187.9	290.2	637	4720			147.1	40.6		22.91	28.51	
W/U	USG	USG		CT	MRI		CT/Angio			CT		USG		CT	

before and after the antiviral therapy (Case 1).

(AST/ALT = Aspartate aminotransferase/Alanine aminotransferase (IU/L), T-BIL=Total bilirubin (mg/dL), PT=Prothrombin time (INR), PLT=Platelet count (K=1000 mm<sup>3</sup>), AFP=alpha-Fetoprotein (ng/mL), W/U=Imaging work up)

the outpatient department had persistently risen. At the time of the admission, he presented with general weakness and loss of appetite, and the vital signs were normal. The initial serology revealed mild hyperbilirubinemia with a total bilirubin of 1.3 mg/dL. The aminotransferase levels were 116 IU/L and 33 IU/L for aspartate (AST) and alanine (ALT) aminotransferase, respectively, with an alkaline phosphatase (ALP) 233 IU/L and  $\gamma$ -glutamyl transpeptidase (GGT) 109 IU/L. The AFP level checked on the admission was 4,720 ng/mL. The HBsAg and anti-HBs tests were negative and nonreactive. The anti-HCV (IgG) was reactive with a titer of 181.14 S/CO and the HCV (PCR) was 4+. A quantitative measurement of HCV-RNA was not carried out. The other serologic findings were normal. He was a type II diabetic and had no history of variceal bleeding, ascites, encephalopathy or any intake of herbs or alcohol

before the admission. He had been followed up at the Department of Gastroenterology of the hospital since May 2002, and the aminotransferase levels checked since then were shown to be gradually increasing, and the AFP levels had increased markedly at the time of her admission (Table 1). As shown in the Table 1, the aminotransferases (AST/ALT) and AFP levels had increased from 57/18 IU/L and 18.1 ng/mL, respectively, in May 2002 to 196/71 IU/L and 4,720 ng/mL, respectively, in February 2003 until the commencement of antiviral therapy. Computed tomography (CT) of the liver taken during the admission showed no definite mass or intrahepatic focal lesion in the liver (Figure 1A). There were no other clinically significant abnormalities found on the CT scan. Hepatic angiography was carried out for the markedly elevated AFP level to rule out any possibility of hepatocellular carcinoma,



**Figure 1.** (A) Computed tomography (CT) of liver demonstrates liver cirrhosis with splenomegaly. No definite mass in liver is seen. No other clinically significant abnormality is noted (Case 1). (B) Post-lipiodol CT scan of the liver shows neither lipiodol staining remaining in the liver parenchyma nor any interval change of liver cirrhosis (Case 1).

**Table 2.** Aminotransferases and alpha-Fetoprotein levels in the hepatitis B patient with liver cirrhosis

Year	2002'					2003'									
	Month/Day	3/22	6/25	11/26	12/27	1/20	2/10	2/24	2/27	3/14	4/15	6/10	7/16	10/25	12/24
AST/ALT	37/27	58/43	66/54	65/21		201/36			134/32	77/55	38/26	35/19	26/15	22/13	33/25
T-BIL	0.7	1.0	1.2	0.9		3.1			2.1	1.8	1.1	0.9	1.4	0.6	0.8
PT	1.31	1.23	1.41	1.35		1.58			1.59	1.58	1.35	1.36	1.36	1.23	1.23
PLT	46k	51K	49k			42K			35K				41K	45K	36K
AFP	8.55	13.3	46.7	139.4	180.3	434			5480	4120	195	28.6	12.4	6.67	5.37
W/U	USG	USG	USG	CT	MRI				CT/Angio		CT		USG	CT	

before and after the antiviral therapy (Case 2).

(AST/ALT = Aspartate aminotransferase/Alanine aminotransferase (IU/L), T-BIL=Total bilirubin (mg/dL), PT=Prothrombin time (INR), PLT=Platelet count (K=1000 mm<sup>3</sup>), AFP=alpha-Fetoprotein (ng/mL), W/U=Imaging work up)

but no definite tumor staining was noted in liver parenchyme (Figure 2). The sequentially performed liver biopsy showed severe porto-periportal inflammatory activity, mild lobular inflammatory activity and septal fibrosis, and these findings were compatible with chronic active hepatitis in liver cirrhosis (Figure 3). The post-lipiodol hepatic CT scan taken 2 weeks after the angiography for detecting any hidden tumor also showed no focal lesion or remnant of lipiodol staining in the liver (Figure 1B).

The patient was treated with antiviral therapy of Interferon (IFN) 3 million units three times a week along with Ribavirin 500 mg twice a day, and then the patient was discharged. The aminotransferases (AST/ALT) and AFP levels taken on follow up at the outpatient department after discharge decreased to 89/90 IU/L and 40.6 ng/mL, respectively, over a period of 3 months. He has taken the anti-viral therapy (IFN and Ribavirin) for over 6 months, and the aminotransferase levels have not

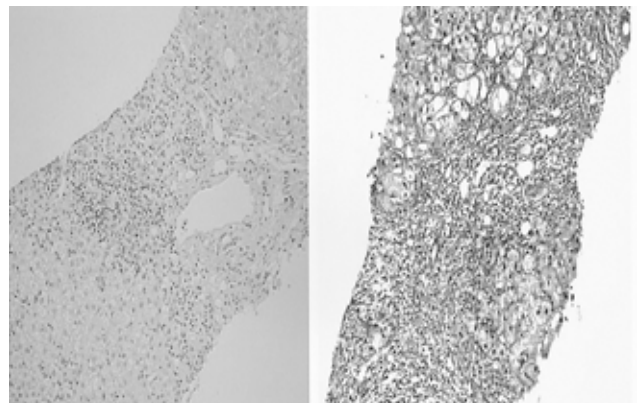
changed significantly, and the AFP level did not increase any further. Moreover, the HCV (PCR) that was checked at the end of the antiviral therapy had converted to 'negative'. During the course of the therapy, follow-up imaging studies, abdominal ultrasonography and liver CT scan were undertaken along with serologic evaluation, and yet no evidence of tumor in the liver parenchyme was discovered.

### Case 2

A 58-year-old female with confirmed hepatitis B-related liver cirrhosis was hospitalized for a detailed evaluation on the hepatic status in February 2003 because the AFP level checked at the outpatient department had tenaciously risen. From March 2002 to February 2003, the aminotransferases levels were slightly elevated, but the AFP level has increased from 8.55 ng/mL in March 2002 to 5,480 ng/mL in February 2003 (Table 2). At the time of the admission, she presented with no specific



**Figure 2.** Hepatic angiography of the liver shows no definite tumor staining in the liver parenchyme. Lipiodol test injection was performed (Case 1).



**Figure 3.** Liver biopsy reveals severe porto-periportal inflammatory activity (4/4), mild lobular activity (2/4) and septal fibrosis (3/4). No evidence of malignancy is found (Left: H&E × 100, Right: V-blue × 100).

complaint. The physical examination showed no abnormalities except mild icteric sclerae. She had no past history of variceal bleeding, ascites, encephalopathy or intake of herbs or alcohol before her admission. The initial serology revealed macrocytic hyperchromic anemia (Hb 11.1 g/dL, Hct 27%) and thrombocytopenia (29,000 mm<sup>3</sup>), moderate hypoalbuminemia (2.7 mg/dL), mild hyperbilirubinemia (total bilirubin 2.3 mg/dL) and elevated aminotransferase levels (AST/ALT 130/42 IU/L). The AFP level checked on the admission was 5,480 ng/mL. The laboratory study on viral markers showed reactive HBsAg/nonreactive Anti-HBs, reactive HBeAg and an HBV-bDNA level of 5,582 pg/mL. A quantitative measurement of HbeAg was not carried out, and the other serologic findings were normal. A liver CT scan carried out during the admission confirmed liver cirrhosis with splenomegaly, ascites and portal hypertension, but there was no mass or focal lesion found in the liver (Figure 4A). There was no definite tumor staining on both lobes of the liver on the hepatic angiography (Figure 5). A liver biopsy could not be carried out on account of the patient's adamant refusal. A post-lipiodol hepatic CT scan was subsequently undertaken 2 weeks after the angiography for detecting any hidden tumor, and it showed neither focal lesion nor lipiodol staining in the liver (Figure 4B). Since the initiation of antiviral therapy with Lamivudine 100 mg once a day, the aminotransferases (AST/ALT) and AFP levels have decreased approximately to 35/19 IU/L and 28.6 ng/mL, respectively, over a period of 3 months. The patient is currently still on the medication as the HBV (PCR) remains positive, but the aminotransferase levels are normal and the AFP level has fallen to 5.37 ng/mL after 9 months of therapy.

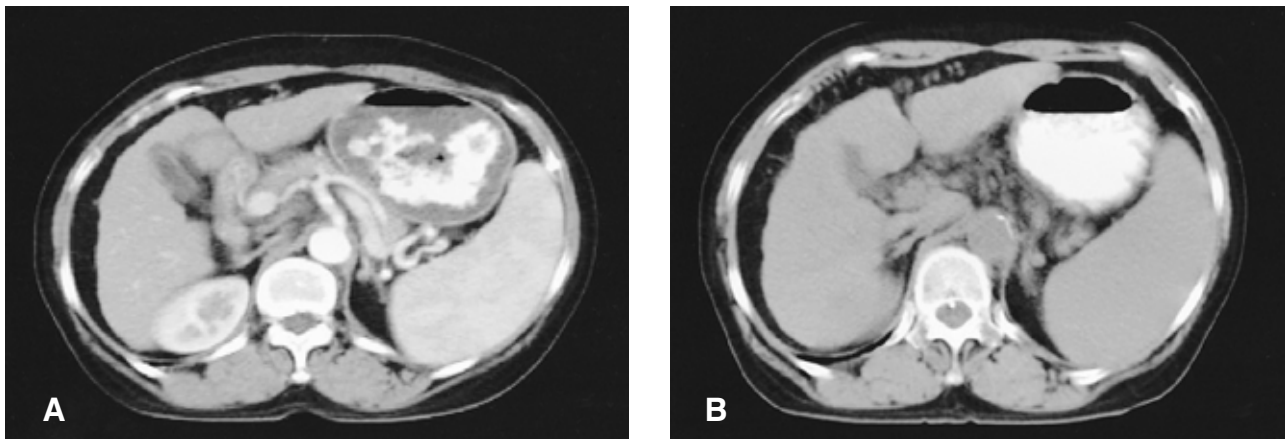
## DISCUSSION

Hepatocellular carcinoma is the seventh most common cancer in men worldwide, and it is the ninth most common cancer in women<sup>1</sup>. Hepatocellular carcinoma develops during the natural history of cirrhosis with the annual incidence being noted at 3 to 10 percent<sup>3, 18</sup>. Since the development of hepatocellular carcinoma is closely associated with chronic liver diseases and particularly liver cirrhosis<sup>2-4</sup>, patients with liver cirrhosis should be regularly examined with imaging techniques such as ultrasonography or computed tomography, and this should be combined with the determination of serum alpha-Fetoprotein, a substance produced by virtually all hepatocellular carcinomas. Close follow-up of such patients with these studies has led to the identification of hepatocellular carcinomas at an early stage, and it makes an optimal therapy possible<sup>3, 5, 19</sup>.

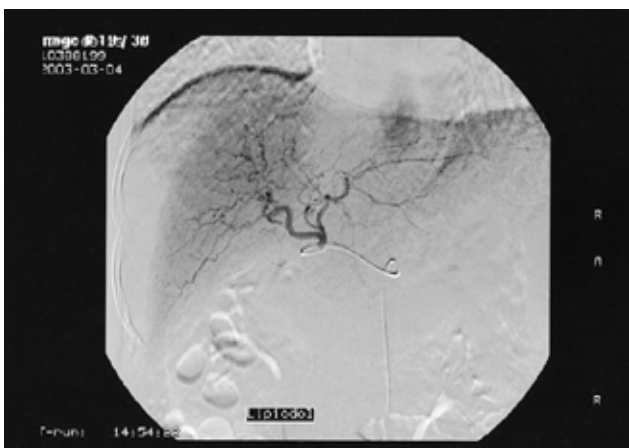
Serum alpha-Fetoprotein concentrations, however, can be elevated both in patients with hepatocellular carcinomas and in

those patients with benign chronic liver diseases, and there is wide overlap between the two groups<sup>6, 7</sup> that causes monitoring with serum alpha-Fetoprotein measurements alone to be insufficient<sup>8, 9</sup>. Alpha-Fetoprotein is a glycoprotein mainly produced by the fetal yolk sac, liver and intestine. Following birth, its production is almost totally repressed and the serum concentration decreases to < 20 ng/mL. Although a low-grade elevation of alpha-Fetoprotein is associated with benign liver diseases, including acute and chronic hepatitis and cirrhosis, those values above 400 ng/mL are often used as a surrogate marker for hepatocellular carcinoma<sup>11</sup>. Human alpha-Fetoprotein has one asparagine-linked biantennary oligosaccharide per molecule<sup>10</sup>. The serum alpha-Fetoprotein of patients with hepatocellular carcinoma is characterized by a greater proportion of alpha-Fetoprotein that reacts with Lens culinaris agglutinin A and erythroagglutinating phytohemagglutinin than the serum alpha-Fetoprotein of patients with benign chronic liver diseases<sup>12-16</sup>. It had been reported that the mean proportion of alpha-Fetoprotein L3 in the patients with cirrhosis and hepatocellular carcinoma at the time of tumor detection was significantly higher than the baseline values in the patients with cirrhosis without hepatocellular carcinoma at baseline<sup>20</sup>. Likewise, these two cases emphasize that only the measurement of AFP is not sufficient for diagnosis of hepatocellular carcinoma, and that it also requires a more specific measurement such as AFP L3 along with imaging studies, especially when the serum AFP level is so high that presence of a tumor needs to be ruled out.

The aminotransferases are also important biological markers that are widely used for liver disease, and they include aspartate aminotransferase (AST, formerly known as SGOT) and alanine aminotransferase (ALT, formerly known as SGPT), which catalyze the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid to produce oxaloacetic acid and pyruvic acid, respectively<sup>17</sup>. Elevation of the activity of these enzymes in serum is believed to result from their leakage from damaged cells, and so this reflects hepatocyte injury. These enzymes are elevated in many forms of liver disease and especially those diseases that are associated with significant hepatocyte necrosis such as acute viral hepatitis, which is the most common cause of massive aminotransferase elevation<sup>17</sup>. The relationship between the levels of aminotransferases and that of AFP is not definite as a rise in the levels of aminotransferase enzymes can be attributable to damage of hepatocytes, while the level of AFP, and especially a markedly increased level (> 400 ng/mL), is rather due to increased production by the genesis of a neoplasm, hepatocellular carcinoma<sup>11, 17</sup>. Moreover, as the extent of elevation of aminotransferases is determined not only by the activity of ongoing diseases such as hepatitis or hepatocellular carcinoma, but also by the underlying hepatic status or reserve, it would be



**Figure 4.** (A) Computed tomography (CT) of liver shows liver cirrhosis with splenomegaly. Presence of ascites and portal hypertension is noted with edema of the small bowel wall. No mass or focal lesion in the liver is seen (Case 2). (B) Post-lipiodol CT scan of the liver demonstrates neither lipiodol staining remaining in the liver parenchyma nor any interval change of liver cirrhosis and splenomegaly (Case 2).



**Figure 5.** Hepatic angiography of the liver shows no definite tumor staining in the liver parenchyma. Lipiodol test injection was performed (Case 2).

irrational to specify any precise relationship between aminotransferases and AFP.

In the two cases described above, the levels of aminotransferases did not increase markedly as compared to their baseline levels and the alpha-Fetoprotein levels. This observation may imply that it is not certain that aminotransferases levels will always increase during acute exacerbation of chronic hepatitis. It could also mean that a change in the enzyme levels may vary depending upon the underlying hepatic status or reserve. In both our cases, however, the extremely high levels of AFP levels created a suspicion for the presence of hepatocellular carcinoma, but the imaging and pathologic studies revealed no evidence of a tumor. It is well known that the AFP level can rise along with hepatic regeneration in viral

hepatitis, but the extent of the AFP levels in the two cases were much greater than what is generally known or expected or had been reported in many other studies. It could be assumed that the rise in alpha-Fetoprotein levels in these cases was due to acute exacerbation of hepatitis as the levels decreased to normal in response to the successful antiviral therapy with conversion of the viral markers to normal as well. Therefore, it could be assumed that significant rise of alpha-Fetoprotein level in acute exacerbation of viral hepatitis in liver cirrhosis not only indicates presence of a tumor but reflects disease activity of hepatitis. More studies on cases like our cases will be required to establish a relationship between AFP level and activity of viral hepatitis including seroconversion, and further investigation will have to be supported by sensitive quantitative measurement of the viral load such as the measurement of HBV-DNA, HbeAg and HCV-RNA, which was not carried out in this study.

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