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Three Cases of Radiation-Induced Hepatitis B Virus Reactivation after Hepatic Tomotherapy: Case Report

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Radiation-induced liver disease (RILD) has been characterized as a veno-occlusive disease with anicteric elevation of alkaline phosphatase (ALP). However, some RILD patients present with elevated transaminase levels rather than with anicteric elevation of ALP, and these findings are common in the Asia-Pacific region where hepatitis B virus (HBV) infection is associated with 70~90% of hepatocelluar carcinoma (HCC) cases. In addition, the development of RILD is more common in patients with hepatitis B virus-related HCC. These findings indicate that susceptibility to RILD might be different in HBV carriers and non-carriers, and moreover, RILD in patients with HBV-related HCC might be associated with another unique pathogenesis such as HBV reactivation. However, HBV reactivation after hepatic irradiation has been reported in only a few studies. This study reports three cases of HBV reactivation after hepatic tomotherapy for management of HCC.

Key Words: Hepatocellular carcinoma, Tomotherapy, Hepatitis B virus reactivation

Radiotherapy (RT) has played a limited role in the management of hepatocellular carcinoma (HCC) and the result is generally unsatisfactory because the liver has a low irradiation tolerance. In recent years, however, computerized RT planning system, three-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT) have been developed, and these techniques markedly reduce radiation exposure of the normal liver. Consequently, the use of RT in patients with unresectable HCC has increased, and these techniques have become an important part of multimodality therapy for HCC.[1] Nevertheless, radiation-induced liver disease (RILD) has been remained one of the most frequently encountered complications, with a reported incidence of 5~39%.[2~5]

RILD has been characterized as a veno-occlusive disease with anicteric elevation of alkaline phosphatase (ALP).[6] However, some RILD patients present with elevated transaminase more often rather than anicteric elevation of ALP, and these findings are especially common in the Asia-Pacific region where hepatitis B virus (HBV) infection is associated with 70~90% of HCC cases.[3,4,7] In addition, several studies have shown that RILD is more common in patients with HBV-related HCC.[3,4,7,8] These findings suggest that the susceptibility to RILD might be different in HBV carriers and non-carriers, and that RILD in patients with HBV-related HCC might be associated with another unique pathogenesis such as HBV reactivation.

HBV reactivation and exacerbation of chronic hepatitis B are well-recognized complications in HBV carriers receiving systemic cytotoxic chemotherapy, immunosuppressive therapy, or transcatheter arterial chemoembolization (TACE).[9~11] Prophylactic antiviral therapy such as lamivudine is, therefore, recommended prior to systemic chemotherapy or immunosuppressive therapy. However, HBV reactivation after hepatic irradiation was reported in only a few studies,[4,8,12] and there is no consensus as to whether prophylactic antiviral agents should be administered to patients with HBV-related HCC before hepatic irradiation.

Here, we report our experiences of HBV reactivation after

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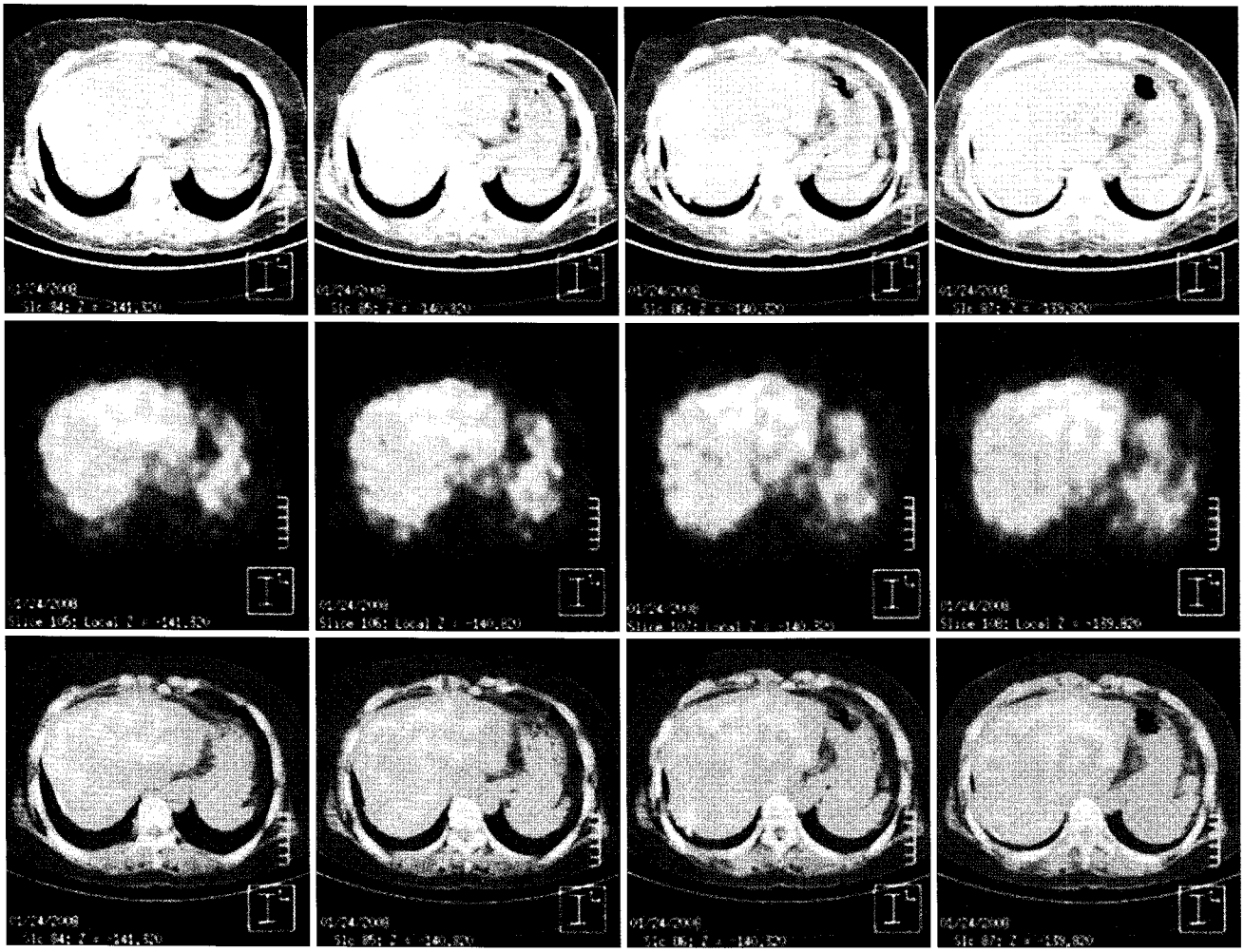

Fig. 1. PET-CT scan of 53 year-old female hepatocelluar carcinoma patient (case 1) before hepatic irradiation. There was diffuse increased ^{18}F-fluorodeoxyglucose uptake in the left lobe and the standard uptake value (SUV) was slightly higher than that of the right lobe (SUV of left lobe, 2.0; SUV of right lobe, 1.5).

hepatic irradiation for HCC.

Case Reports

1. Case 1

A 53 year-old woman was diagnosed as hepatitis B-viral liver cirrhosis in 2002 and HCC in 2003. She received TACE four times, and the last TACE in June 2007. However, in December 2007, HCC recurred in the left hepatic lobe, so she visited the Department of Radiation-Oncology for radiotherapy. A PET-CT scan showed diffuse increased ^{18}F-fluorodeoxyglucose (FDG) uptake in the left lobe and the standard uptake value (SUV) was slightly higher than that of the right lobe (Fig. 1). On serologic examination, the levels of aspartate aminotransferase (AST) and α-fetoprotein were increased above normal range but other serologic findings were within normal ranges (AST, 51 U/L; alanine aminotransferase [ALT], 27 U/L; α-fetoprotein, 53.39 ng/mL; total bilirubin, 0.91 mg/dL; ALP, 92 U/L; prothrombin time [PT] INR, 1.03%). Polymerase chain reaction (PCR) for HBV DNA showed that the level of HBV DNA was 79 IU/mL (415 copies/mL). The Child-Pugh classification was Class A.

Radiotherapy was performed on the diffuse HCC in the left hepatic lobe using tomotherapy from February to March 2008. We delivered a total dose of 60 Gy with a daily dose of 3 Gy. The respiratory movement estimated by fluoroscope and the planning target volume (PTV) margins were 1~2 cm around the clinical target volume (CTV). The volume of

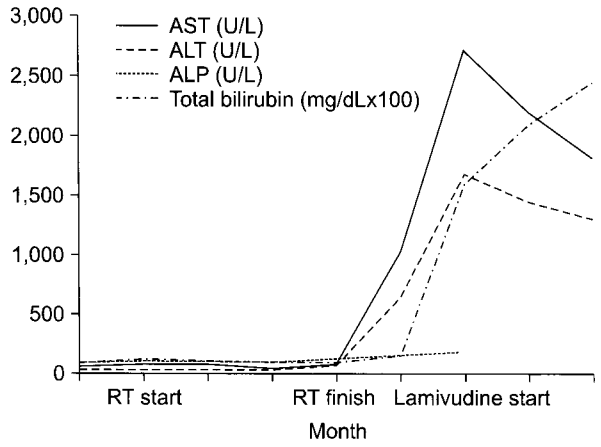

Fig. 2. Sequential serologic data of 53 year-old female hepatocelluar carcinoma patient (case 1). After irradiation, the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin were markedly elevated. After administration of lamivudine for treatment of hepatitis B reactivation (2.5 months after tomotherapy), the levels of AST and ALT were decreased rapidly, however, the level of total bilirubin was elevated more and more. RT: radiotherapy, ALP: alkaline phosphatase.

non-neoplastic normal liver was defined as the whole liver volume excluding the gross tumor volume (GTV). A dose-volume histogram was generated and the V_{30} and V_{20} values were 29% and 39%, respectively.

During tomotherapy, we checked the levels of liver enzymes (AST, ALT), ALP, and total bilirubin weekly. The levels of AST were higher than the normal range and were maintained within the range of 47~78 U/L. The other serologic findings were maintained within normal range. There were no severe acute complications during radiotherapy.

One month after tomotherapy, the patient did not complain of any discomfort. The levels of liver enzymes were increased above normal range (AST, 69 U/L; ALT, 48 U/L) and the levels of ALP and total bilirubin were also increased, but remained within normal range (ALP, 117 U/L; total bilirubin, 0.92 mg/dL). On the PET-CT scan performed at 2 months after tomotherapy, the diffuse FDG uptake in the left lobe of the liver had disappeared. However, we observed whole body jaundice and icteric sclera. The levels of liver enzymes were markedly increased (AST, 1,000 U/L; ALT, 625 U/L) and the levels of ALP and total bilirubin were also increased above normal range (ALP, 149 U/L; total bilirubin, 1.49 mg/dL). At 2.5 months after tomotherapy, jaundice was aggravated and the patient complained of abdominal discomfort. We also observed the ascites. The levels of liver enzymes were further increased (AST, 2,716 U/L; ALT, 1,679 U/L) and the levels of ALP and total bilirubin were also increased (ALP, 175 U/L; total bilirubin, 2.9 mg/dL). The level of PT INR was also increased (3.18%). PCR for HBV DNA showed that, the level of HBV DNA was increased to 123,000 IU/mL (646,980 copies/mL). There were no possible etiologic factors for HBV reactivation other than hepatic irradiation. We confirmed HBV reactivation and started antiviral therapy (lamivudine, 100 mg daily). After initiation of antiviral therapy, the levels of AST and ALT were decreased rapidly, however, the level of total bilirubin continued to rise (Fig. 2), and ultimately she died 3 days later (79 days after tomotherapy).

2. Case 2

A 72 year-old man was diagnosed as a HBV carrier in 1990 and HCC in 1998. He received TACE six times and the last TACE in February 2010. However, in March 2010, HCC recurred in hepatic segments 2 and 6, and he visited Department of Radiation-Oncology for radiotherapy. An abdominal CT scan showed a lipiodolized nodule with viable tumor in segment 6, and a probable HCC-like mass in segment 2 (Fig. 3). On serologic examination, the levels of AST, ALT, ALP, and PT INR were slightly elevated above normal range (AST, 53 U/L; ALT, 45 U/L; ALP, 144 U/L; PT INR, 1.27%) and the level of total bilirubin was within normal range (0.66 mg/dL). The Child-Pugh classification was Class A.

Radiotherapy was performed on two HCC masses in segments 2 and 6 using tomotherapy from March to April 2010. We delivered a total dose of 50 Gy with a daily dose of 2.5 Gy. The respiratory movement estimated by fluoroscope and the PTV margins were 1~1.5 cm around the CTV. The volume of non-neoplastic normal liver was defined as the whole liver volume excluding GTV, and the V_{30} and V_{20} values were 13% and 40%, respectively.

During radiotherapy, the levels of liver enzymes, ALP, and total bilirubin were checked weekly. The levels of AST and ALT were decreased to normal ranges and maintained within normal ranges during radiotherapy. The levels of total bilirubin were also maintained within normal range. However, the levels of ALP further increased and maintained within the range of 193~219 U/L. There were no severe acute

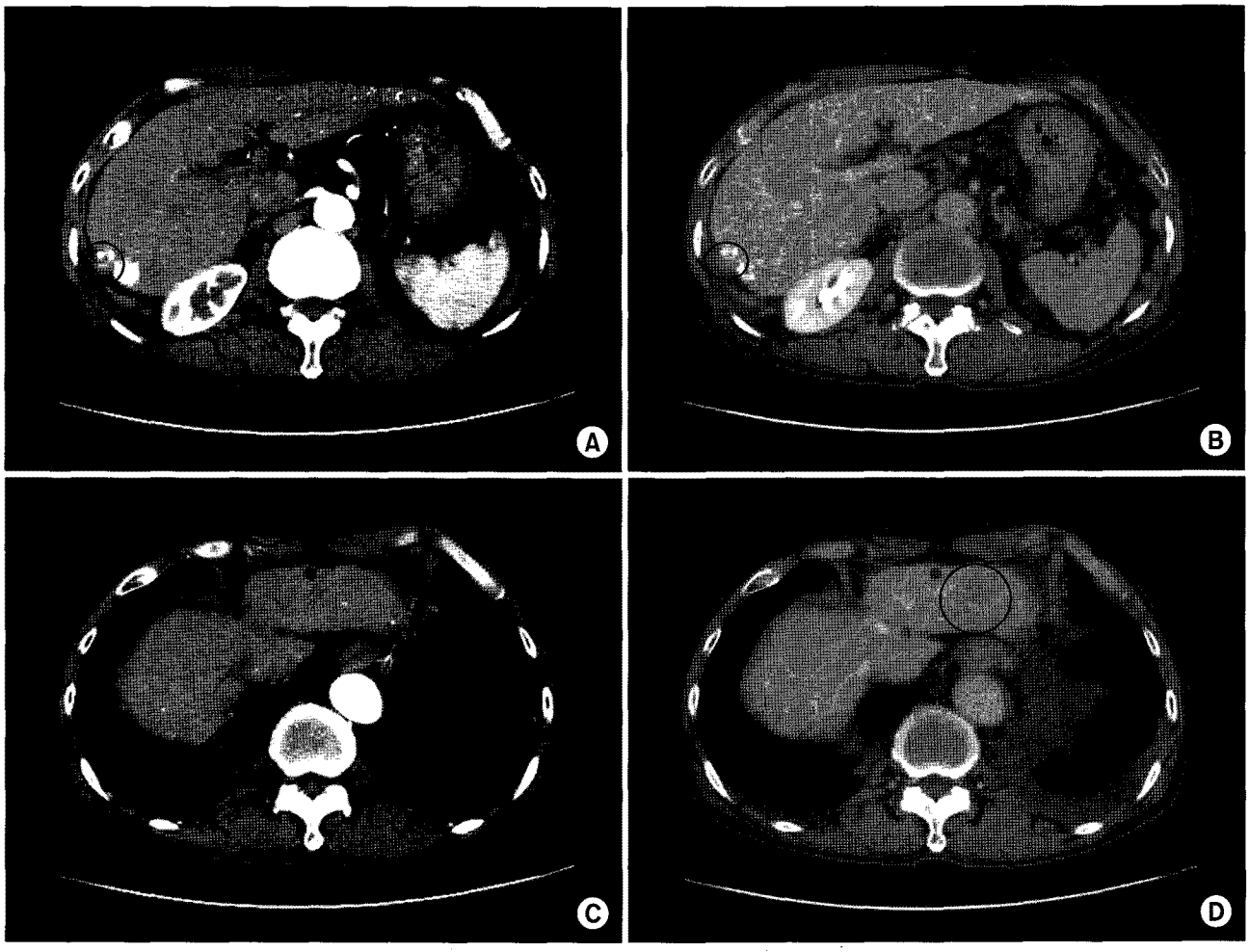

Fig. 3. Abdominal CT scan of 72 year-old male hepatocelluar carcinoma (HCC) patient (case 2) before hepatic irradiation. (A) There was lipiodolized nodule with viable tumor in segment 6. On arterial phase, the nodule was enhanced (black circle). (B) There was lipiodolized nodule with viable tumor in segment 6. On delayed phase, the nodule washed out (black circle). (C) There was probable HCC-like mass in segment 2. On arterial phase, the mass was not enhanced. (D) There was probable HCC-like mass in segment 2. On delayed phase, the mass washed out (black circle).

complications during tomotherapy.

One month after tomotherapy, the patient complained of mild general weakness. The levels of liver enzymes were elevated above normal range (AST, 124 U/L; ALT, 74 U/L). The level of total bilirubin increased compared with the level during tomotherapy, but was within normal range (1.07 mg/dL). The level of ALP was still elevated above normal range, but was similar to the level during tomotherapy (187 U/L). An abdominal CT scan performed at 2 months after tomotherapy revealed no definitive findings of viable tumor on the previous RT sites of segments 2 and 6. However, we found a new HCC lesion in the inferior part of the previously irradiated nodule in segment 6. The levels of liver enzyme were further elevated (AST, 358 U/L; ALT, 199 U/L) as were the levels of ALP and total bilirubin (ALP, 244 U/L; total bilirubin, 1.83 mg/dL). At 2 months and 7 days after tomotherapy, jaundice developed and the patient complained of general weakness and loss of appetite. On serologic examination, the levels of liver enzymes and ALP were decreased (AST, 161 U/L; ALT, 130 U/L; ALP, 243 U/L), however, the level of total bilirubin was further increased (5.06 mg/dL), and the level of PT INR was increased compared with the level before tomotherapy (2.11%). PCR for HBV DNA showed that, the level of HBV DNA was increased to 5,787 IU/mL (33,677 copies/mL). We suspected HBV reactivation and chronic hepatitis B exacerbation, and

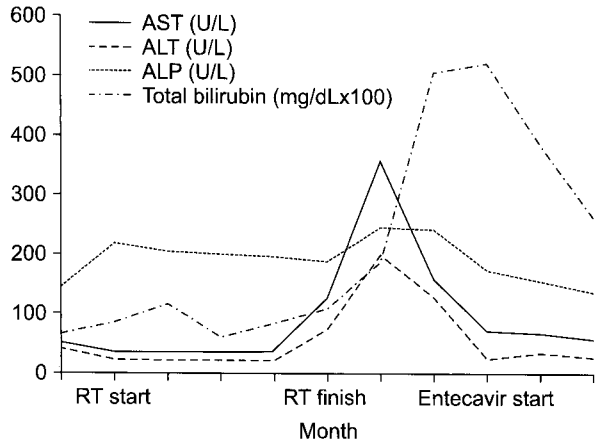

Fig. 4. Sequential serologic data of 72 year-old male hepatocelluar carcinoma (HCC) patient (case 2). After irradiation, the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin were markedly elevated and alkaline phosphatase (ALP) was slightly elevated. After administration of entecavir for treatment of hepatitis B reactivation (2 months and 7 days after tomotherapy), the levels of liver enzyme and ALP were decreased to within normal range, and the level of total bilirubin also decreased but still above normal range. RT: radiotherapy.

started antiviral therapy (entecavir, 0.5 mg daily). At 10 days after initiation of antiviral therapy, the levels of liver enzymes and ALP decreased to near normal range (AST, 73 U/L; ALT, 26 U/L; ALP, 173 U/L), and the level of PT INR also slightly decreased (2.02%). However, the level of total bilirubin was increased slightly (5.21 mg/dL). At 1 month after initiation of antiviral therapy, the levels of AST, ALP and PT INR further decreased (AST, 67 U/L; ALP, 153 U/L; PT INR, 1.96%) and the level of ALT increased slightly compared with the previous serologic examination, but was within normal range (33 U/L). In addition, the level of total bilirubin markedly decreased (3.88 mg/dL). At 2.5 month after initiation of antiviral therapy, the levels of liver enzymes and ALP decreased to within normal range, and the level of total bilirubin decreased further but remained above normal range (2.61 mg/dL) (Fig. 4). The patient is awaiting TACE for treatment of the new HCC in segment 6.

3. Case 3

A 60 year-old man was diagnosed as a HBV carrier in 1986 and HCC in 2006. He received TACE three times and the last TACE was done in November 2009. However, in March 2010, new HCC lesions developed in segments 3 and 7. And he visited the Department of Radiation-Oncology for radiotherapy. Liver MRI showed two small nodular lesions with viable HCC in segments 3 and 7 (Fig. 5). On serologic examination, the values of AST, ALT, ALP, total bilirubin, and PT INR were all within normal range (AST, 36 U/L; ALT, 20 U/L; ALP, 100 U/L; total bilirubin, 0.67 mg/dL; PT INR, 1.07%). PCR for HBV DNA showed that, the level of HBV DNA was 29 IU/mL (153 copies/mL). The Child-Pugh classification was Class A.

Radiotherapy was performed on the two HCC lesions in segments 3 and 7 using tomotherapy from May to June 2010. We delivered a total dose of 60 Gy with a daily dose of 2.4 Gy. The respiratory movement estimated by fluoroscope and the PTV margins were 1.2~1.8 cm around the CTV. The volume of non-neoplastic normal liver was defined as the whole liver volume excluding GTV, and the V_{30} and V_{20} values were 15% and 33%, respectively.

During radiotherapy, the levels of AST, ALT, ALP, and total bilirubin were checked weekly. All serologic findings were maintained within normal range (AST, 29~32 U/L; ALT, 17~24 U/L; ALP, 112~120 U/L; total bilirubin, 0.63 ~0.65 mg/dL). There were no severe acute complications during tomotherapy.

At 15 days after tomotherapy, he did not complain of any discomfort. On serologic examination, the levels of AST and ALT were elevated above normal range (AST, 62 U/L; ALT, 75 U/L). The levels of ALP and total bilirubin were similar to those during tomotherapy and within normal range (ALP, 108 U/L; total bilirubin, 0.72 mg/dL). At 1 month after tomotherapy, the patient complained of general weakness. On serologic examination, the levels of AST, ALT, ALP, total bilirubin, and PT INR were all elevated (AST, 413 U/L; ALT, 467 U/L; ALP, 159 U/L; total bilirubin, 0.89 mg/dL; PT INR, 1.42%). At 1.5 months after tomotherapy, we performed a liver MRI. There was no enhanced lesion on the arterial phase, and no definitive viable HCC at the previous RT site, in segments 3 and 7. However, we found icteric sclera, and all serologic findings were markedly aggravated (AST, 1,286 U/L; ALT, 1,024 U/L; ALP, 208 U/L; total bilirubin, 1.92 mg/dL; PT INR, 1.60%). We suspected radiation-induced HBV reactivation, and measured the HBV DNA by PCR, which showed that the level of HBV DNA was increased to 75,600 IU/mL (440,000 copies/mL). There were no possible

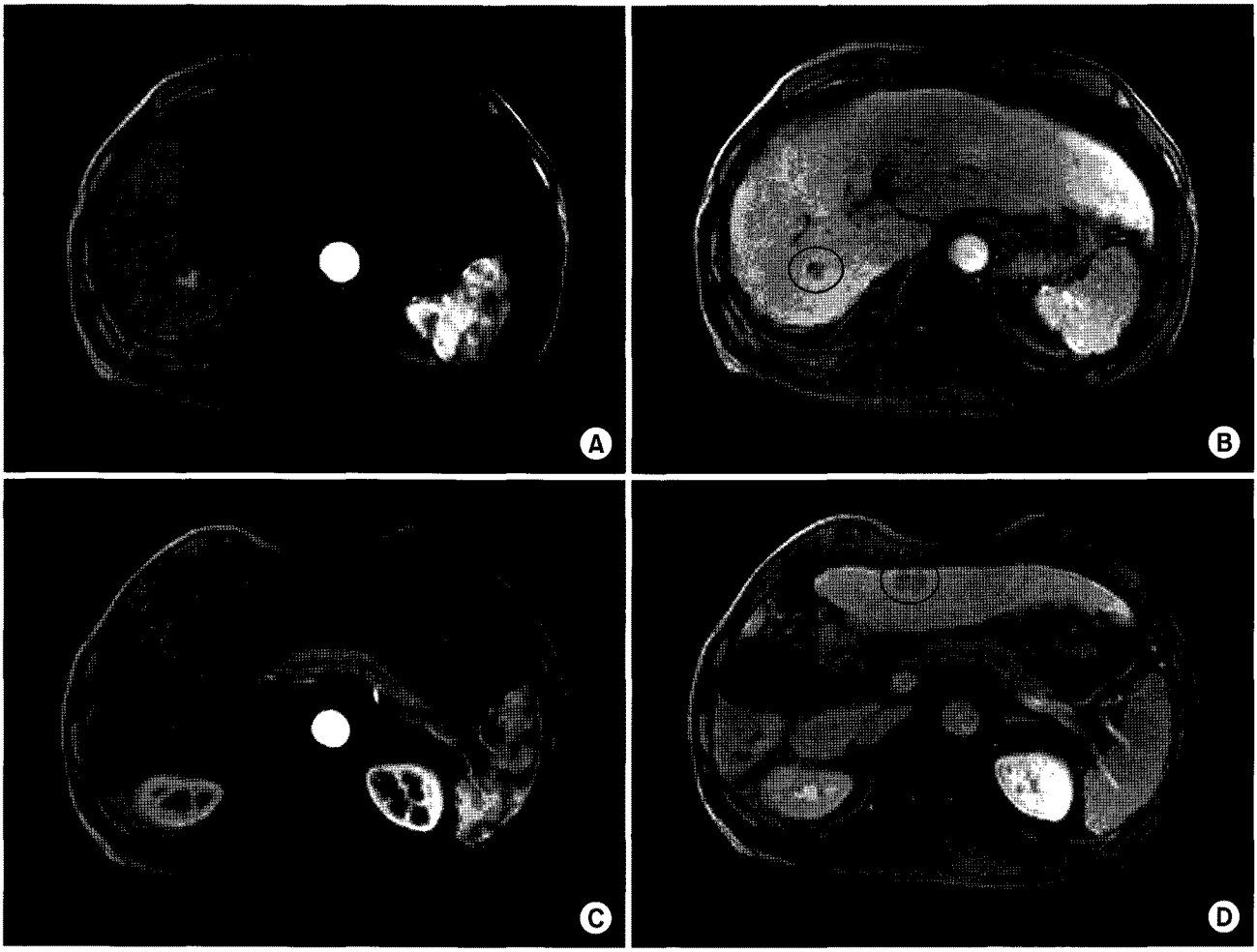

Fig. 5. Liver MRI of 60 year-old male hepatocelluar carcinoma (HCC) patient (case 3) before hepatic irradiation. (A) There was small nodular lesion with viable HCC in segment 7. On arterial phase, the mass was enhanced (black circle). (B) There was small nodular lesion with viable HCC in segment 7. On delayed phase, the mass was showed as low signal intensity (black circle). (C) There was small nodular lesion with viable HCC in segment 3. On arterial phase, the mass was slightly enhanced (black circle). (D) There was small nodular lesion with viable HCC in segment 3. On delayed phase, the mass showed low signal intensity (black circle).

etiologic factors for HBV reactivation other than tomotherapy. We confirmed HBV reactivation and started antiviral therapy (entecavir, 0.5 mg daily). At 10 days after initiation of antiviral therapy, we detected whole body jaundice. The levels of AST, ALT, ALP, and PT INR markedly decreased (AST, 269 U/L; ALT, 284 U/L; ALP, 118 U/L; PT INR, 1.45%), however, the level of total bilirubin was markedly elevated (19.02 mg/dL). After 17 days from initiation of antiviral therapy, the levels of AST, ALT, and ALP further decreased (AST, 200 U/L; ALT, 134 U/L) and the level of ALP was within normal range (101 U/L). However, the level of PT INR was elevated again (1.60%) and the level of total bilirubin was further elevated (19.67 mg/dL) and jaundice was aggravated. After 25 days from initiation of antiviral therapy, the levels of AST, ALT and ALP further decreased (AST, 190 U/L; ALT, 112 U/L; ALP, 99 U/L) and the level of total bilirubin also decreased (17.74 mg/dL). However, the level of PT INR was further elevated (1.77%) (Fig. 6).

He is continuously receiving antiviral therapy for management of radiation-induced HBV reactivation and consequential exacerbation of chronic hepatitis B. Important characteristics of these three cases are summarized in Table 1.

Discussion

RILD, also called radiation hepatitis, has been reported as

one of the most common treatment-related complications in patients receiving hepatic irradiation. The main pathologic finding of RILD is veno-occlusive disease, which occurred mainly in the portal vein system, and consequential marked venous congestion in the central portion of each lobule, and atrophy of hepatocytes adjacent to the congested veins. However, the underlying pathophysiology of RILD is not well understood. Endothelial cell injury, tumor growth factor-β1, tumor growth factor-β3, and tumor necrosis factor-α have been suspected to implicate in the pathogenesis of RILD. Whatever the reason, RILD has clinical characteristics of anicteric hepatomegaly, ascites, and elevated liver enzymes (ALP more than the transaminases) developing 2 weeks to 3 months after hepatic irradiation.[13] However, some RILD patients present with jaundice and elevated transaminases more often rather than anicteric elevation of ALP. These findings are particularly common in the Asia-Pacific regions, where 70 ~90% of HCC patients have underlying HBV infection.[3,4,7] In addition, several studies have shown that RILD development is more common in patients with hepatitis B virus-related HCC.[3,4,7,8] For these reasons, some authors argued that RILD in patients with HBV-related HCC might be associated with another unique pathogenesis and the possible unique pathogenesis might be HBV reactivation.

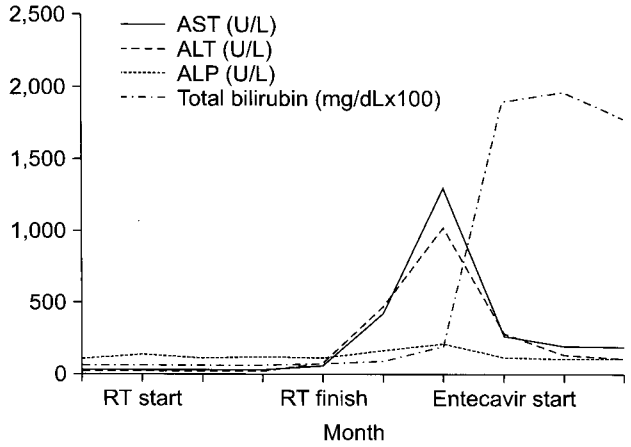

Fig. 6. Sequential serologic data of 60 year-old male hepatocelluar carcinoma (HCC) patient (case 3). During tomotherapy, all serologic findings were maintained within normal range. After irradiation, the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin were markedly elevated and alkaline phosphatase (ALP) was slightly elevated. After administration of entecavir for treatment of hepatitis B reactivation (1.5 months after tomotherapy), the levels of AST and ALT were decreased markedly and the level ALP decreased to within normal range. However, the level of total bilirubin maintained high. RT: radiotherapy.

Actually, Kim et al.[8] investigated whether hepatic irradiation influences HBV reactivation and chronic hepatitis B exacerbation in patients with HBV-related HCC. In their study, a total of 48 HCC patients with underlying HBV

Table 1. Characteristics of Three Patients with Radiation-induced Hepatitis B Virus Reactivation

Case no.	1	2	3
Irradiated site	Left hepatic lobe	Segment 2 Segment 6	Segment 3 Segment 7
Radiation dose (total dose/daily dose)	60 Gy/3 Gy	50 Gy/2.5 Gy	60 Gy/2.4 Gy
Interval between RT* termination and confirmation of HBV† reactivation	2 mo 14 day	2 mo 7 day	1 mo 15 day
Pre-RT serologic findings			
AST‡ (U/L)	51	53	36
ALT§ (U/L)	27	45	20
ALP‖ (U/L)	92	144	100
Total bilirubin (mg/dL)	0.91	0.66	0.67
Serologic findings at RT termination			
AST (U/L)	47	38	32
ALT (U/L)	29	21	24
ALP (U/L)	86	193	116
Total bilirubin (mg/dL)	0.87	0.84	0.65
Serologic findings at confirmation of HBV reactivation			
AST (U/L)	2,716	161	1,286
ALT (U/L)	1,679	130	1,024
ALP (U/L)	175	243	208
Total bilirubin (mg/dL)	2.9	5.06	1.92

*radiotherapy, †hepatitis B virus, ‡aspartate aminotransferase, §alanine aminotransferase, ‖alkaline phosphatase.

infection underwent 3D-CRT to the liver, and the rate of HBV reactivation was significantly increased after hepatic irradiation (21.8%) ($p<0.05$). Because treatment for RILD is supportive management whereas treatment of HBV reactivation is antiviral therapy such as lamivudine, the authors suggested that HBV reactivation and consequential chronic hepatitis B exacerbation should be differentially diagnosed from RILD.

In our case report, case 1 and 3 showed markedly elevated levels of total bilirubin, AST, and ALT after hepatic tomotherapy compared with those before tomotherapy. The levels of ALP were also elevated, but were not markedly high. Most of all, the levels of HBV DNA were increased to very high level after hepatic tomotherapy compared with those before tomotherapy. So we could confirm radiation-induced HBV reactivation. In case 2, there was no baseline HBV DNA level before irradiation, and the levels of AST and ALT were not markedly increased after tomotherapy. However, after tomotherapy, the levels of total bilirubin were elevated, and the level of HBV DNA was checked to 5,787 IU/mL. Despite the definite evidences which support confirmation of radiation-induced HBV reactivation were sparse, we strongly suspected that radiation-induced HBV reactivation is major cause of post-tomotherapy abnormal hepatic function.

The underlying pathophysiology of radiation-induced HBV reactivation is poorly understood. According to Chou et al.,[14] the release of interleukin-6 from irradiated endothelial cells is associated with radiation-induced HBV reactivation through the signal transducer and activator of transcription 3 signal transduction pathway. However, the exact pathophysiology is not known at present.

Furthermore, the risk factors for HBV reactivation after hepatic irradiation have not been identified. Kim et al.[8] investigated the risk factors for HBV reactivation after hepatic irradiation, but could not find significant differences in age, gender, AST or ALT level, hepatitis B envelope antigen (HBeAg) positivity, serum HBV DNA level, or radiation dose between patient groups. Although there is no study which identified risk factors for HBV reactivation after irradiation, several studies have reported risk factors for HBV reactivation after chemotherapy.[15,16] These studies reported that patients with high baseline HBV DNA level and HBeAg positivity are at risk of HBV reactivation after chemotherapy. Because HBV reactivation and consequent chronic hepatitis B exacerbation can be treated by antiviral therapy, patients who have the above risk factors might be carefully monitored during and after irradiation. Moreover, further studies should be carried out to identify risk factors for HBV reactivation after irradiation.

It is well established that HBV reactivation and exacerbation of viral hepatitis B can occur after cytotoxic chemotherapy.[9~11,17,18] Therefore, prophylactic antiviral therapy is recommended prior to cytotoxic chemotherapy in patients who are HBV carriers.[19,20] Yeo et al.[19] recommended daily treatment with 100 mg lamivudine, commencing 7 days before the start of chemotherapy, and continuing throughout the course of chemotherapy and for 8 weeks after discontinuation of chemotherapy. However, in radiotherapy, there is no consensus as to whether prophylactic antiviral agents should be administered or not, and if so, what regimen should be applied. Therefore, further studies are necessary to clarify the benefits and most effective regimens of prophylactic antiviral therapy for prevention of radiation-induced HBV reactivation.

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국문초록

간암의 토모테라피 후 발생한 B형 간염 바이러스 재활성화 3예: 증례보고

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방사선간염은 대개 황달을 동반하지 않은 알칼리인산 분해효소(alkaline phophatase)의 상승을 특징으로 보인다. 하지만, 방사선간염 환자의 일부에서는 아미노전달효소(transaminase)의 상승을 특징적인 소견으로 보이고, 이러한 소견은 특히 간암 환자의 70~90%가 B형 간염 바이러스 보균자인 아시아 지역에서 흔하게 관찰된다. 또한 B형 간염 바이러스 보균자인 간암 환자를 방사선으로 치료했을 때 방사선간염이 더 흔하게 발생한다. 이런 사실들은 B형 간염 바이러스 보균자에서 방사선간염의 발생 기전이 비보균자에서의 그것과 다를 수 있다는 것을 시사하고, B형 간염 바이러스 보균자에서 발생하는 방사선간염의 발생기전은 B형 간염 바이러스의 재활성화와 연관이 있을 것으로 추측된다. 하지만, 현재 간암의 방사선치료 후 B형 간염 바이러스의 재활성화에 대한 연구는 미미한 수준이다. 이에 저자들은 간암 환자의 토모테라피 후 발생한 B형 간염 바이러스 재활성화 3예를 보고하고자 한다.

핵심용어: 간암, 토모테라피, B형 간염 바이러스 재활성화