

Radiation-induced hepatitis B virus reactivation in hepatocellular carcinoma: A case report

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Abstract. Hepatitis B virus (HBV) reactivation associated with radiotherapy is rare. The present study reports the case of a 46-year-old man that experienced fatal HBV reactivation. The patient suffered from hepatocellular carcinoma (HCC) with portal vein tumor thrombus, which was treated by radiotherapy at a daily fraction of 2 Gy over 5 weeks, up to a total radiation dose of ~50 Gy. The patient presented with fatigue, yellow sclera and abdominal distension ~8 weeks subsequent to the administration of radiotherapy. The liver function tests, including the level of total bilirubin and prothrombin time, suggested acute-on-chronic liver failure. The serum HBV-DNA level had also increased between undetectable levels and 7.2×10^4 copies/ml. Although the present patient with HCC was treated with 0.5 mg/day entecavir for 8 weeks, in addition to radiotherapy, radiation-induced HBV reactivation occurred. The condition of the patient worsened gradually. The present study emphasizes the importance of liver function and HBV-DNA screening and pre-emptive antiviral prophylaxis prior to radiotherapy in patients with HCC.

Introduction

Hepatitis B virus (HBV) infection is a serious and common global public health problem (1). It is conservatively estimated that >2 billion individuals have been infected with HBV worldwide and 350 million have suffered from chronic HBV infection. In Asia and the majority of Africa, the disease is particularly prevalent and usually acquired perinatally or in childhood (1). In total, 15-40% of the infected patients will

develop cirrhosis, liver failure or hepatocellular carcinoma (HCC), which is currently the fifth most frequent cancer and accounts for between 300,000 and 500,000 mortalities per year (2).

Curative surgery is currently available for only 10% of patients. Due to the low tolerance of the liver for irradiation, radiotherapy is limited and is therefore not optimal for the treatment of HCC (3). Therefore, chemotherapy has become a main palliative treatment for certain inoperable patients. However, there is a considerable probability for the reactivation of HBV in HCC patients that receive chemotherapeutic drugs, which may be a fatal complication and may lead to disruption in treatment schedules (4). With the development of novel radiotherapy as 3-dimensional conformal therapy or stereotactic radiation therapy, the role of radiotherapy has become of increasing importance in the treatment of HCC, particularly for HCC patients with portal vein tumor thrombus (PVTT) or a tumor diameter <10 cm (3-5).

To the best of our knowledge, previous studies have reported the occurrence of chemotherapy-associated reactivation of HBV in the literature (6,7). However, the occurrence of radiotherapy-associated HBV reactivation is rare. Therefore, the present study reports the case of a patient that experienced fatal HBV reactivation during radiotherapy for HCC with portal vein tumor thrombosis (PVTT) formation.

Case report

A 46-year-old male patient with a long history as a HBV carrier presented with fatigue, yellow sclera and abdominal distension that had lasted for >10 days was referred to the First Affiliated Hospital of Anhui Medical University (Hefei, Anhui, China) on June 26, 2012. The patient possessed a family history of chronic HBV infection and a history of alcohol abuse. The patient had been diagnosed with HBV-associated HCC at the First Affiliated Hospital of Zhengzhou University (Zhengzhou, Henan, China) in April 2012.

Abdominal computed tomography with contrast medium revealed a left frontal tumor, 8.7 cm in diameter, in the liver with PVTT. The total liver volume of the patient was 1617.4 cm³ and the gross tumor volume was 352.7 cm³. The patient was identified to possess the following pattern of HBV markers: Hepatitis B surface antigen (HBsAg)-positive;

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anti-hepatitis B surface antibody (HBsAb)-negative; hepatitis B envelope antigen (HBeAg)-negative; anti hepatitis B envelope antibody (HBeAb)-positive; and anti hepatitis B core antibody (HBcAb)-positive. The quantitative polymerase chain reaction (qPCR) level of HBV-DNA remained undetectable. The biochemical analyses of liver function tests revealed normal function, as follows: Alanine aminotransferase (ALT), 26 U/l (normal, 7-40 U/l); aspartate aminotransferase (AST), 20 U/l (normal, 13-35 U/l); total bilirubin (TB), 17.34 $\mu\text{mol/l}$ (normal, 5-19 $\mu\text{mol/l}$); and prothrombin time (PT), 15.6 sec (normal, 11-16 sec). The patient received prophylactic antiviral therapy with oral administration of the nucleoside analog entecavir (0.5 mg/day over 8 weeks) in addition to undergoing radiotherapy, commencing on May 1, 2012. The patient was administered with a daily fraction of 2 Gy, up to a total radiation dose of ~ 50 Gy over 5 weeks.

On June 26, 2012, ~ 8 weeks subsequent to the first dose of radiotherapy, the patient was admitted to the Department of Infectious Diseases at the First Affiliated Hospital of Anhui Medical University due to fatigue, yellow sclera and abdominal distension that had lasted >10 days. The liver function tests revealed severe liver dysfunction, as follows: Albumin, 29.3 g/l (normal, 40-50 g/l); ALT, 741 U/l (normal, 7-40 U/l); AST, 405 U/l (normal, 13-35 U/l); TB, 356.15 $\mu\text{mol/l}$ (normal, 5-19 $\mu\text{mol/l}$); and PT, 57.5 sec (normal, 11-16 sec). The HBV serology status continued to indicate that the patient was HBsAg-positive, HBeAb-positive, HBcAb-positive, HBsAb-negative and HBeAg-negative. However, the detectable qPCR level of HBV-DNA was 7.2×10^4 copies/ml. The laboratory characteristics for infection with the hepatitis A, C, D or E viruses were absent. As entecavir demonstrates few side-effects on liver function, the nucleoside analogue was not considered to be the cause of the changes in liver function.

On the basis of the symptoms, physical signs and laboratory examination, the patient was diagnosed with acute-on-chronic liver failure resulting from the reactivation of HBV. The patient received prompt symptomatic and supportive treatment for liver dysfunction in addition to active antiviral therapy. The duration of antiviral therapy was ~ 8 weeks from May 2012. However, the liver failure was further aggravated by the HBV reactivation. The breathing and circulation of the patient gradually weakened; on June 27, the second day subsequent to admission, the patient demonstrated acute thoracodynia, dyspnea and mania. The blood gas analysis revealed a PaO₂ level of 55 mmHg, PaCO₂ level of 30 mmHg and P_{A-a}O₂ level of 0.86 kPa. The patient succumbed to HBV reactivation at 3 weeks after the end of radiotherapy.

Discussion

HBV reactivation is a common problem that clinicians often encounter following chemotherapy or immunosuppressive therapy for disorders including hematological or solid malignancies, rheumatism and systemic lupus erythematosus. Chemotherapy-associated reactivation has been well described in the literature. Induced immunosuppression facilitates an increased viral load and antigen expression. Upon recovery of the immunity of the patient subsequent to treatment withdrawal or reduction, there is an intense immune-mediated response that eradicates HBV-infected hepatocytes and manifests clinically

as asymptomatic anicteric hepatitis, severe hepatitis or even fatal liver failure (8). The aforementioned hypothesis may not apply to the pathogenesis of radiation-induced HBV reactivation due to the differences between radiotherapy and chemotherapy, and since radiotherapy usually exerts an increased effect on local tissue rather than the whole immune system.

HBV reactivation is a severe complication that occurs in patients with HCC that undergo radiotherapy, and it may occasionally be fatal. Although the present patient with HCC was treated with entecavir in addition to radiotherapy, radiation-induced HBV reactivation occurred and led to the development of liver failure. The mortality rate directly due to HBV reactivation has been reported as $\sim 60\%$ in previous studies (7,9-11). Therefore, awareness of this potentially life-threatening complication and regular monitoring of the clinical parameters associated with HBV reactivation during chemotherapy or radiotherapy are of considerable importance (12). To the best of our knowledge, HBV reactivation during chemotherapy is associated with baseline HBV-DNA levels and HBeAg positivity. Few studies have investigated the risk factors and incidence of HBV reactivation in patients with HBV-associated HCC undergoing radiotherapy (13). However, a recent study reports that the serum HBV-DNA level and certain dosimetric parameters, such as normal liver volume, gross tumor volume and mean radiological dose, acted as prognosis factors for HBV reactivation and should be considered carefully prior to radiotherapy (14).

The present study indicated that preemptively prophylactic administration of entecavir prior to the performance of radiotherapy may be proposed as a first-line preventive therapy in patients with HCC that are inactive carriers of HBV, rather than as a preventive therapy once radiotherapy has commenced or as a rescue therapy when HBV reactivation has occurred. The optimal duration of entecavir administration for the prevention of radiotherapy-induced HBV reactivation has yet to be clarified. In the future, large prospective and case-controlled studies should be performed to determine the optimal duration. A previous study reported that an increased and persistent interleukin (IL)-6 density in the liver was evident following radiotherapy. IL-6 was released from irradiated endothelial cells and induce HBV reactivation *in vitro* and *in vivo* through the bystander effect. The signal transducer and activator of transcription 3 signaling pathway mainly plays an important role in this phenomenon reported from the literature (13). As a result, the additional studies are also required to delineate the precise mechanism on HBV reactivation subsequent to radiotherapy.

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