Reactivation of Hepatitis B Virus After Glioblastoma Treatment With Temozolomide
—Case Report—

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Abstract
A 61-year-old man with glioblastoma and positive for hepatitis B surface antigen (HBsAg) developed acute hepatitis due to hepatitis B virus (HBV) reactivation after concomitant postoperative treatment with temozolomide (75 mg/m2/day) and radiation therapy (60 Gy in 30 fractions). Corticosteroids were not used during chemo-radiation therapy, and grade 4 lymphocytopenia was observed. The levels of liver function tests (LFTs), including levels of aspartate aminotransferase and alanine aminotransferase, increased 5 weeks after the completion of chemo-radiation therapy, and reached the maximum levels of 1,549 IU/l (normal 13 to 33 IU/l) and 1,653 IU/l (normal 8 to 42 IU/l), respectively, after 2 weeks. At this point, serum HBV-deoxyribonucleic acid (DNA) level had increased to 630-fold over the baseline, and therapy with the antivirus agent entecavir (0.5 mg daily) was started. Over the next 2 weeks, the levels of LFTs and HBV-DNA improved. The present and previous cases suggest that grade 3/4 lymphocytopenia or grade 2 lymphocytopenia with corticosteroid use might have a significant effect on HBV reactivation. To avoid this complication, HBsAg-positive patients with glioblastoma should consult a hepatologist for initiating antivirus therapy before temozolomide treatment.

Key words: hepatitis B virus, reactivation, glioblastoma, temozolomide, immunosuppression

Introduction
The reactivation of hepatitis B virus (HBV) is a well-recognized complication of cytotoxic chemotherapy for malignant disease. HBV reactivation usually occurs in patients with hematological malignancies, but is also known in patients with solid tumors, including breast cancer, gastrointestinal cancer, and lung cancer.12 Temozolomide is an alkylating agent that exerts cytotoxic activity by inducing deoxyribonucleic acid (DNA) damage and apoptosis of tumor cells,7 and is part of the standard postoperative chemotherapy for the treatment of glioblastoma.9 Temozolomide carries the risk of HBV reactivation,12 but few cases of temozolomide-induced HBV reactivation have been reported, so the incidence and associated risk factors, and the optimal management of glioblastoma patients with chronic HBV infection remain unclear.

We treated a patient with glioblastoma who was positive for hepatitis B surface antigen (HBsAg) and developed acute hepatitis due to HBV reactivation during temozolomide treatment, and discuss the management of patients with glioblastoma who have chronic HBV infection.

Case Report
A 61-year-old man presented with generalized convulsions. He had been informed of his HBV carrier status but had not received any treatment. On admission, he tested positive for HBsAg and hepatitis B envelope (HBe) antibody, and negative for HBe antigen, hepatitis C virus antibody, and human immunodeficiency virus. The blood HBV-DNA concentration was 105 copies/ml. Magnetic resonance imaging of the brain showed a tumor in the bilateral frontal lobes involving the corpus callosum (Fig. 1A). The patient presented with slight disorientation and left hemiparesis. Partial tumor removal was achieved through a right frontal craniotomy, and the histological diagnosis was glioblastoma (Fig. 1B). Betamethasone 8 mg was intravenously administered for 3 days following the operation. Ten days after resection, local radiation therapy (60 Gy in 30 fractions over 6 weeks) and temozolomide chemotherapy (75 mg/m2/day) were initiated. Before chemotherapy and radiotherapy, the liver function tests (LFTs) were normal: aspartate aminotransferase (AST) was 26 IU/l (normal 13 to 33 IU/l), and alanine aminotransferase (ALT) was 28 IU/l (normal 8 to 42 IU/l). During chemo-radiation therapy, the lowest measured white blood cell count was 2900/μl, absolute neutrophil count was 2240/μl, and absolute lymphocyte
count was 190/µl. Four weeks after the completion of chemo-radiation therapy, the levels of LFTs started to increase, and one week later continued to deteriorate. AST increased to 685 IU/l and ALT increased to 744 IU/l. At this time we consulted with a hepatologist to determine the cause of the LFT changes. Abdominal computed tomography (CT) with contrast medium revealed a mass lesion in the liver (Fig. 2). Alpha fetoprotein (AFP) and protein induced by vitamin K antagonists-II (PIVKA-II) were elevated to 257.6 ng/ml (normal < 10.0 ng/ml) and 8,349 mAU/ml (normal < 40 mAU/ml), respectively.

Our diagnosis was hepatocellular carcinoma (HCC) that had possibly developed before temozolomide treatment. Further, since the HCC was not obstructing the bile duct, we thought that the HCC was not the cause of the LFT changes. The patient’s medication regimen at initial presentation consisted of valproic acid, propranolol, and famotidine. After the LFT changes, we stopped administration of famotidine but continued valproic acid and propranolol. The HBV-DNA level increased to 10^5.8 copies/ml. On the basis of the laboratory data and radiological findings, we determined that temozolomide-induced HBV reactivation was the main cause of the LFT changes and acute hepatitis, although the possibility of drug-induced hepatitis or HCC-related LFT change was not completely excluded. Accordingly, we started treatment with the antivirus agent entecavir (0.5 mg daily). For 5 days after the start of entecavir treatment, AST and ALT continued to increase to the maximum levels of 1,549 IU/l and 1,653 IU/l, respectively, but thereafter improved markedly. Two weeks after the start of entecavir treatment, the LFTs returned to almost normal levels. The HBV-DNA level also decreased to 10^1.8 copies/ml (Fig. 3).

After normalization of the LFTs, we started treatment with adjuvant temozolomide at 150 mg/m² daily for 5 days/28 days while continuing entecavir therapy. The second cycle used 200 mg/m² daily for 5 days/28 days, and no further elevation of LFTs and HBV-DNA level was observed, even though the lowest lymphocyte count was 110/µl (Fig. 3). Four weeks after the onset of LFT changes, the levels of AFP and PIVKA-II were 405.2 ng/ml and 10,195 mAU/ml, respectively, and continued to exacerbate his condition. Transarterial embolization was performed for the treatment of HCC. Three weeks later, the patient’s AFP and PIVKA-II levels improved, decreasing to 166.4 ng/ml and 182 mAU/ml, respectively. However, after sec-

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Fig. 1 A: Preoperative T₁-weighted magnetic resonance image with contrast medium showing a tumor in the bilateral frontal lobes involving the corpus callosum. B: Photomicrograph of the tumor specimen showing glioblastoma with cellular anaplasia and prominent microvascular proliferation. Hematoxylin and eosin stain, original magnification ×200.

Fig. 2 Abdominal computed tomography scan with late phase contrast enhancement showing a low density mass lesion of 9-cm diameter in the liver.

Fig. 3 Time courses of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lymphocytes, and hepatitis B virus-deoxyribonucleic acid (HBV-DNA) levels. Four weeks after completion of concomitant temozolomide and radiation therapy (RT + TMZ), AST and ALT began to increase and continued to increase to a maximum of 1,549 IU/l and 1,653 IU/l, respectively. HBV-DNA level increased to 10^5.8 copies/ml. After entecavir administration, ALT, AST, and HBV-DNA levels improved during the ensuing 2 weeks. After normalization of liver function, two cycles of adjuvant temozolomide (arrows) were initiated while continuing entecavir, without further elevation of AST and ALT even though the lowest lymphocyte count was 110/µl.
ond transarterial embolization, he developed conscious disturbance, and was transferred to a nursing hospital 6 months after the completion of chemo-radiation therapy. Twelve months after the neurosurgical operation, he died of glioblastoma progression.

Discussion

The reactivation of HBV by immunosuppressive agents is characterized by increased levels of serum HBV-DNA, abnormal LFTs, and clinical hepatitis of varying degrees of severity, which may result in death. HBV reactivation occurs in 38–48% of HBsAg-positive patients with lymphoma or other hematological malignancies, who are undergoing conventional therapies, including cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). The risk factors for HBV reactivation include male sex, young age, steroid use, anthracycline use, high pre-chemotherapy HBV-DNA level, and diagnosis of lymphoma or breast cancer. Two possible mechanisms may explain HBV reactivation during chemotherapy: immunosuppression enhances virus replication, leading to hepatic toxicity, or chemotherapy-induced T-cell depletion dampens the host response to viral antigens, which enables broader hepatocyte infection, and following the subsequent withdrawal of cytotoxic chemotherapy, a rebound immune response results in hepatocyte destruction.

HBV reactivation-induced hepatitis has been defined as an increase in HBV-DNA level to 10-fold or more when compared with the baseline level, or as an absolute increase in HBV-DNA level to more than 1,000 × 10^6 genome equivalents/ml in the absence of other systemic infections. In our patient, the HBV-DNA level increased by 630-fold over the baseline, when the LFTs were elevated, indicating HBV reactivation. However, we could not completely exclude the possibility of drug-induced hepatitis or HCC-related LFT elevation, because the patient had received medication (valproic acid, propranolol, and famotidine) during chemotherapy just before the LFT changes and had underlying HCC. However, the patient continued to receive valproic acid and propranolol even after the LFTs were elevated. Abdominal CT did not reveal bile duct stenosis due to HCC, and both the LFTs and HBV-DNA level improved shortly after entecavir treatment before HCC therapy. Therefore, we presume that the possibility of drug-induced hepatitis or HCC-related increase in LFTs is much lower than that of HBV reactivation, although famotidine-induced hepatitis remains much less likely. Famotidine is also known to induce agranulocytosis and can cause immunosuppression. However, the lowest white blood cell count and absolute neutrophil count in our patient were 2900/μl and 2240/μl, respectively, so the possibility of famotidine-induced agranulocytosis leading to HBV reactivation was thought to be quite low.

HBV infection is one of the causative factors in the development of HCC, and the patient probably had HCC before temozolomide treatment. However, HCC was unlikely to be involved in the development of HBV reactivation after temozolomide treatment, because HCC was localized at the time of increases in LFTs and did not impair the patient’s general condition, including the immune system.

Only two cases of HBV reactivation after temozolomide treatment for glioblastoma have been reported (Table 1). A 65-year-old woman with glioblastoma presented with HBV reactivation on day 27 of cycle 3 of adjuvant temozolomide therapy and died 2 weeks after the onset. She had a remote history of hepatitis B infection but did not undergo hepatitis examination before starting treatment. She did not receive steroid medication before the onset of HBV reactivation, and her lowest lymphocyte count was 450/μl. A 50-year-old HBsAg-positive man with glioblastoma presented with HBV reactivation 5 weeks after the completion of concomitant radiotherapy and temozolomide. He was successfully treated with the antiviral agent lamivudine over the ensuing 7 weeks. He was treated with 4 mg of dexamethasone during radiation therapy and 2 mg just before the onset of HBV reactivation. His lowest lymphocyte count was 580/μl. Our patient developed the symptoms 4 weeks after completing concomitant radiotherapy and temozolomide, and was successfully treated with entecavir during the ensuing 2 weeks. He had no steroid exposure before the onset of HBV reactivation, and his lowest lymphocyte count was 190/μl. All these cases suggest that grade 3/4 lymphocytopenia or grade 2 lymphocytopenia with corticosteroid use might have a significant effect on the development of HBV reactivation. The guidelines issued in the Joint Report of the Intractable Liver Disease Study Group of Japan and the Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis recommend that all patients should be screened for HBsAg, and anti-hepatitis B core and anti-HBs antibodies before chemotherapy is initiated. HBsAg-positive patients should be advised to consult a hepatologist for initiating antiviral therapy, such as entecavir before starting chemotherapy.

HBV reactivation after chemotherapy with temozolomide may be a rare complication. However, temozolomide is associated with CD4+ T-cell dysfunction and therefore may cause increased susceptibility to opportunistic infections by agents such as Pneumocystis pneumonia. This characteristic immunosuppression may also induce HBV reactivation. In the Japanese population, 1.4% of individuals are positive for HBsAg, so HBV reactivation during glioblastoma treatment with temozolomide may become a critical issue. To avoid this complication, patients with glioblastoma should be screened for hepatitis B, and HBsAg-positive patients should be referred to a hepatologist for initiating antivirus therapy before starting temozolomide treatment. Moreover, HBV reactivation should be included in the differential diagnosis of patients with elevated LFTs.

References

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<th>Author (Year)</th>
<th>HBV status</th>
<th>Diagnosis</th>
<th>Onset</th>
<th>Status of hepatitis</th>
<th>WBC</th>
<th>Neutrophil</th>
<th>Lymphocyte</th>
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<th>Steroid</th>
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<td>remote history of HBV infection, HBsAg (+)</td>
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<td>190</td>
<td>273.5</td>
<td>stop 3 days after operation</td>
<td>successfully treated with entecavir</td>
<td>50</td>
<td>M</td>
<td>5</td>
<td>27</td>
<td>3</td>
<td>450</td>
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<td>Chheda et al. (2007)</td>
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<td>GBM</td>
<td>4 weeks after completion of TMZ</td>
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<td>2240</td>
<td>190</td>
<td>152.6</td>
<td>stop 3 days after operation</td>
<td>successfully treated with lamivudine</td>
<td>65</td>
<td>F</td>
<td>remote history of HBV infection, HBsAg (+)</td>
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<td>5 weeks after completion of TMZ concomitant with RT</td>
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<td>Present case</td>
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<td>5 weeks after completion of TMZ concomitant with RT</td>
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F: Female, GBM: Glioblastoma, HBsAg: hepatitis B surface antigen, M: male, N/A: not available, RT: radiation therapy, WBC: white blood cell.


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