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CASE REPORT

Hepatitis B virus reactivation associated with temozolomide for malignant glioma: a case report and recommendation for prophylaxis

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Abstract Hepatitis B virus (HBV) reactivation during anticancer chemotherapy or immunosuppressive therapy in chronic carriers can lead to fatal liver failure. We report a rare case of severe HBV reactivation during postoperative radiotherapy with concomitant and adjuvant temozolomide (TMZ) for malignant glioma. A 49-year-old Japanese woman with a history of HBV carrier status with positive results for hepatitis B surface antigen presented with persistent headache due to a tumor in the left frontal lobe. The tumor was partially resected and anaplastic astrocytoma was diagnosed. Postoperative liver function was normal and radiotherapy plus concomitant and adjuvant TMZ was started. Impaired liver function became apparent just before administration of adjuvant TMZ, and acute liver failure developed. Antiviral therapy including entecavir, a nucleoside analog, led to a successful outcome and the patient survived. This case underlines the possibility of HBV reactivation due to TMZ and suggests the utility of HBV screening and antiviral prophylaxis before administration of TMZ to patients with malignant glioma.

Keywords Hepatitis B · Malignant glioma · Nucleoside analog · Prophylaxis · Reactivation

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Introduction

Recent development of chemotherapy and immunosuppressive therapy has improved the prognosis for cancer patients. Severe hepatitis due to reactivation of hepatitis B virus (HBV) is well known as a significant complication in cancer patients treated with cytotoxic chemotherapy and/or immunosuppressive therapy, especially in combination with corticosteroids [1–5]. In the treatment of malignant gliomas, temozolomide (TMZ) was introduced in the second half of the 1990s and is now widely used in combination with radiotherapy as one of few effective drugs [6, 7]. As TMZ can be administered orally and has a low frequency of severe adverse events compared with previous chemotherapeutic agents, physicians may tend to use this therapy 'with an easy mind'. We describe here a case of a HBV carrier with malignant glioma that presented with severe acute hepatitis due to HBV reactivation during administration of a standard regimen using TMZ combined with radiotherapy. To the best of our knowledge, this represents the third report in the literature of HBV reactivation associated with TMZ during the treatment of malignant gliomas [8, 9].

Case report

A 49-year-old Japanese woman with a history of HBV carrier status presented with headache that had persisted for months. Neurological examination revealed no abnormalities, but radiological examination identified a left frontal tumor with compression of the lateral ventricles. On magnetic resonance (MR) imaging, the lesion showed a partially enhanced area after administration of gadolinium (Fig. 1a). Serological examination on admission showed

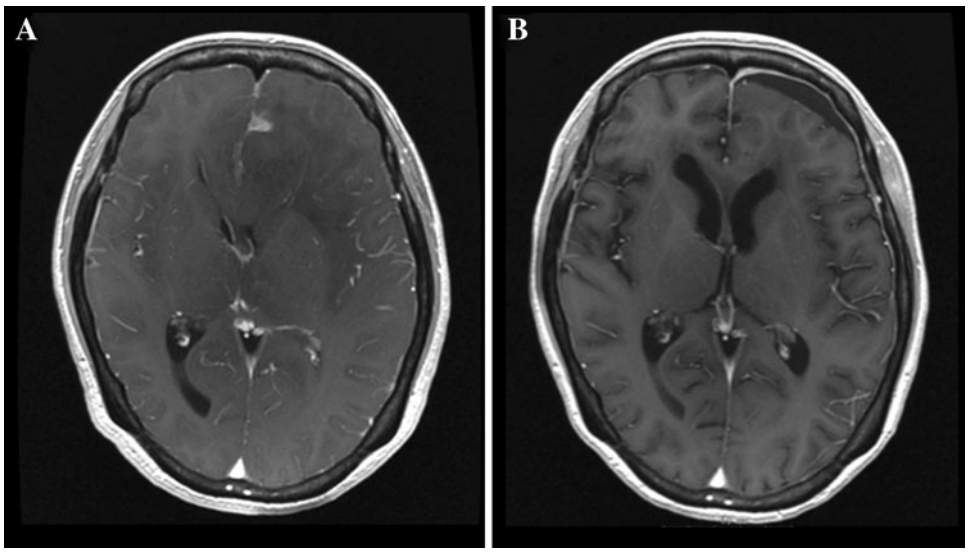

Fig. 1 Gadolinium-enhanced T1-weighted magnetic resonance (MR) images. **a** Preoperative MR image showing a left frontal tumor with partially enhanced lesion. **b** Six months after partial resection of the tumor and radiotherapy plus concomitant temozolomide, no residual tumor is apparent

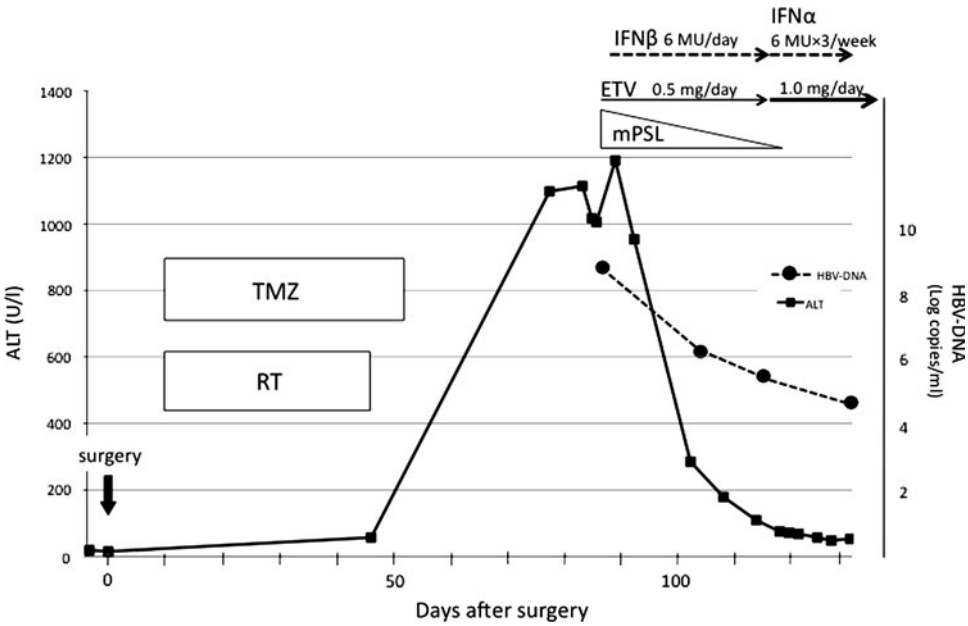

Fig. 2 Profile of the patient during the course of surgery and radiotherapy plus concomitant temozolomide. The patient experienced severe acute hepatitis 75 days after first administration of temozolomide (*TMZ*). Antiviral therapy reduced alanine aminotransferase (*ALT*) levels to within the normal range, while the serum HBV-DNA titer remained high despite a gradual reduction. Normal ranges of ALT and HBV-DNA are as follows: <40 U/l and <2.6 log copies/ml, respectively. *ETV* entecavir, *IFN* interferon, *mPSL* methylprednisolone, *MU* megaunits, *RT* radiotherapy

positive results for hepatitis B surface antigen (HBsAg), but results of liver function tests were normal. The patient underwent partial resection of the tumor and histopathological examination of the resected specimen led to a diagnosis of anaplastic astrocytoma. Ten days postoperatively, radiotherapy was initiated (54 Gy in 27 fractions) with concurrent administration of TMZ at a dose of 75 mg/m^2 for 42 days. Corticosteroids were not used during the course of treatment. The postoperative course during chemoradiotherapy was clinically uneventful, except for grade 3 or 4 hematotoxicity with nadir of leukocytes 1280/μl, neutrophils 605/μl, and lymphocytes 169/μl. She was discharged well from hospital 39 days after first administration of TMZ. Seventy-five days after first administration of TMZ, she reported general feelings of fatigue and was hospitalized with worsening of liver function: alanine aminotransferase, 1098 U/l; aspartate aminotransferase, 1044 U/l; serum total bilirubin, 1.4 mg/dl; alkaline phosphatase, 515 U/l; and prothrombin time, 33%. Serological examination showed positive results for HBsAg, hepatitis B core antibody (anti-HBc) and hepatitis Be antibody (anti-HBe), and negative results for hepatitis B surface antibody (anti-HBs) and HBe antigen. Serum HBV-DNA titer was more than 9 log copies/ml (over the measurable limit), consistent with reactivation of HBV. We started steroid pulse therapy using methylprednisolone and interferon. In addition we also administered entecavir initially at a dose of 0.5 mg/day. Results of liver function tests improved and HBV-DNA titer gradually decreased (Fig. 2). The patient continues to receive entecavir at a dose of 1.0 mg/day and

has not yet restarted administration of TMZ. However, MR images at 6 months postoperatively revealed complete remission of the tumor (Fig. 1b).

Discussion

Achieving complete cure of malignant glioma using only tumor resection is difficult and therefore chemoradiotherapy is principally employed as an adjuvant therapy. TMZ, a new oral cytotoxic alkylating agent, represented a major therapeutic advance in the treatment of malignant gliomas in the latter half of 1990s. Radiotherapy plus concomitant and adjuvant TMZ has been recognized worldwide as a standard initial treatment for glioblastoma. The trials demonstrated that this regimen is well tolerated with mild hematotoxicity during the course, but showing grade 3/4 lymphocytopenia with high frequency, being seen in 79% of patients during the concomitant radiotherapy plus TMZ phase [6, 7].

The risk of HBV reactivation in chronic carriers undergoing chemotherapy or immunosuppressive therapy has been well known for over 35 years, mainly in patients with hematological malignancies [1]. In association with the development of anticancer treatments, this complication has also been recognized in patients with solid cancers. Previous reports have estimated the incidence of HBV reactivation in HBsAg-positive patients undergoing anticancer chemotherapy at over 20% [4, 5]. The incidence is particularly high among patients with lymphoma, at 32–78% [10, 11], while the incidence is reported to be nearly 20% in patients with solid cancer [4, 5]. Clinical manifestations of this condition are diverse, ranging from asymptomatic liver enzyme elevation to fatal liver failure. The mortality rate directly due to HBV reactivation is approximately 60% in more recent investigations [12]. Furthermore, even when the cancer patient recovers from hepatitis, interruption of chemotherapy may reduce survival.

The mechanisms underlying HBV reactivation have been speculated as follows [13]. Cytotoxic chemotherapy or immunosuppressive therapy results in escape of HBV from immune surveillance, leading to viral replication in hepatocytes. With the subsequent withdrawal of therapy, a rebound immune response mainly by cytotoxic T-lymphocyte causes abrupt hepatocyte destruction. Meanwhile, the HBV-DNA sequence contains the glucocorticoid-responsive element, through which corticosteroids directly stimulate HBV gene expression [14]. Regimens including corticosteroids, especially for lymphomas, thus carry a great risk of HBV reactivation. The recent advent of newer monoclonal antibodies with profound and long-lasting immunosuppressive effects, such as rituximab, an anti-CD20 agent, has frequently induced HBV reactivation not only in HBV carriers, but also in HBsAg-negative patients [15].

Given the increasing incidence of this problem, guidelines for preventing chemo- or immunosuppressive therapy-induced HBV reactivation have been proposed [2, 16–19]. In these guidelines, screening for both HBsAg and anti-HBc is essential for prediction of HBV reactivation, and HBV screening is recommended for all patients prior to chemo- or immunosuppressive therapy for solid cancer as well as hematological malignancies. HBsAg- or anti-HBc-positive patients have a risk of HBV reactivation and should undergo further complete serological examination including of HBV-DNA titers, which can be measured by polymerase chain reaction (PCR) assay. According to the latest guideline proposed by the Japanese Ministry of Health, Labor and Welfare [19], a prompt real-time PCR assay is especially recommended for patients who are HBsAg-negative but anti-HBc-postive and/or anti-HBs-positive. Even if the HBV-DNA is undetectable, the monitoring of HBV-DNA titers by PCR assay should be continued once a month during treatment. Patients with HBsAg-positive findings or detectable HBV-DNA require pre-emptive antiviral therapy. Standard antiviral agents presently consist of nucleoside analogs. Among these, entecavir is preferred if longer treatment (>12 months) with chemotherapy or immunosuppressive therapy is anticipated. Interferon remains one of the first-line options for patients without cirrhosis [17]. The optimal duration of prophylactic therapy with nucleoside analogs has yet to be established. Patients are generally recommended to continue prophylaxis for at least 1 year and preferably 2 years after completion of cancer chemotherapy or immunosuppressive therapy [20].

HBV reactivation during malignant glioma treatment with TMZ seems rare and only two cases have been reported to date [8, 9]. These two cases, a 50-year-old man [8] and 65-year-old woman [9] both with glioblastoma, underwent treatment of the same regimen as the present case. In the former case, he had been on dexamethasone 4 mg/day and presented with worsening of liver function 76 days after the first administration of TMZ. He recovered successfully with the administration of lamivudine as a nucleoside analog. In the latter case, she had not been on corticosteroid during the administration of TMZ; however, she presented with acute liver failure on day 27 of the third cycle of adjuvant TMZ (200 mg/m^2) or 125 days after the first administration of TMZ, and died within 2 weeks even with the administration of entecavir.

HBV infection is a global public health problem and more than 350 million are chronic carrier [21]; the majority (75%) of whom live in endemic areas such as China and Southeast Asia [21]. In Japan, the number of HBV-infected persons is estimated to be 1 million, or about 0.8% of the

total population, and the prevalence is highest in the group of 60–69 years, especially with HBV genotype C [22]. HBV genotype A infection, which is liable to become chronic, has recently been reported to be increasing at a younger age by sexual contact [23]. In this situation, HBV reactivation with antiglioma therapy would be expected to become more of problem in Japan as well as worldwide. In the present case, despite mild myelosuppression and no use of corticosteroids in the course of treatment with TMZ, HBV reactivation occurred. Even though hematological toxicity associated with TMZ itself is relatively mild, the possibility of HBV reactivation should be kept in mind, as the period for administration of TMZ is usually prolonged in the treatment of malignant gliomas and corticosteroids are frequently used concurrently to diminish peritumoral edema. To avoid this potentially fatal hepatic flare, HBV screening and antiviral prophylaxis during TMZ therapy should be considered in reference to the guidelines.

Conclusion

HBV reactivation is an old and new problem along with the development of anticancer chemotherapy or immunosuppressive therapy. It is important to prevent the occurrence of this fatal condition, as antiviral agents are nowadays available and effective. HBV screening is recommended in all patients that will undergo TMZ therapy for malignant gliomas.

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Conflict of interest No author has any conflict of interest.

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