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Glioblastoma multiforme and hepatitis B: do the right thing(s)

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Abstract. – OBJECTIVE: Hepatitis B virus (HBV) reactivation is a well-known complication related to immunosuppression.

Clinical manifestations of HBV relapse range from self-limiting anicteric hepatitis to acute hepatic failure.

Temozolomide (TMZ) is an alkylating agent used for the treatment of glioblastoma multiforme (GBM), the most common and deadliest of malignant primary brain tumors.

CASE REPORT: We report the case of a 52-year old man with a history of serological positivity for hepatitis B surface antigen (HBsAg) who was diagnosed with GBM. Since the tumor was multifocal and thus inoperable, the patient received radiotherapy with concomitant TMZ and corticosteroids, without a prophylactic therapy for HBV infection. Acute hepatitis developed five months later the beginning of anticancer therapy. We started antiviral entecavir, which led to a decrease of HBV-DNA titer to 20 IU/ml, allowing the prosecution of the TMZ therapy.

CONCLUSIONS: Up to now only four other cases of HBV relapse during TMZ therapy have been reported in literature. These cases underline the need of HBV screening and antiviral prophylaxis before starting TMZ administration.

Key Words:
Glioblastoma multiforme, Hepatitis B reactivation, Oncology, Temozolomide, Chemotherapy.

Introduction

It is estimated that one third of the world population has serological characteristics of past or recent hepatitis B virus (HBV) infection and that around 350-400 million people are chronically infected[1]. Patients infected with HBV are exposed to reactivation in case of immunosuppression due to drugs used for autoimmune disorders, hematological and solid tumors and organ transplantation. Reactivation usually develops at the time of immune reconstitution as a consequence of the destruction of HBV-infected hepatocytes[2]. Clinical consequences of HBV reactivation range from self-limiting anicteric hepatitis to acute hepatic failure[3].

The alkylating agent temozolomide (TMZ) is currently the drug of choice for the treatment of glioblastoma multiforme (GBM). TMZ exerts its cytotoxic activity by inducing DNA damage and apoptosis of tumor cells[4]. TMZ treatment has been associated with HBV reactivation only in a limited number of GBM cases and it is still not clear how these patients should be managed. Priorities in these cases are two-fold: to manage and control the hepatitic process and to guarantee the continuation of the oncologic treatment.

Since TMZ can be administered orally and has a low percentage of side effects, physicians may tend to use it too easily, without performing a screening for infectious diseases.

We report the case of HBV reactivation in a man with GBM who had been treated with radiotherapy, concomitant TMZ and glucocorticoids.

Case Report

A 52-years old man presented with upper quadrants abdominal pain. Years before he had been informed about the serological positivity for hepatitis B surface antigen (HBsAg) and he had been given the diagnosis of inactive carrier (IC) since HBV-DNA titer was < 2000 IU/ml and aminotransferases and ultrasound were repeatedly normal, thus treatment of HBV infection had never been considered.

Five months earlier he had been diagnosed with multifocal inoperable GBM (anaplastic astrocytoma, grade 3 according to the World Health

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Organization classification)[5]. Before starting GBM treatment, HBV screening was not performed. He was initially treated with radiotherapy (1.67 Gy/day for five days/week) and concurrent oral administration of TMZ at the dose of 75 mg/m^2 for forty days. Dexamethasone was also administered as anti-edema agent at a maximum dose of 16 mg/day. Later, he was treated with oral TMZ only. In the first cycle (5 days/28 days) TMZ was given at the dose of 150 mg/m^2, while in the second cycle (5 days/28 days) the dose was increased to 300 mg/m^2. Dexamethasone was also administered at the dose of 8 mg/day during both cycles. One month after the end of the second cycle he was admitted to our Department because of abdominal pain.

Hematochemical evaluations showed altered liver function tests (LFTs): aspartate aminotransferase (AST) 263 IU/l, alanine aminotransferase (ALT) 1114 IU/l, gamma-glutamyl transpeptidase (gamma-GT) 145 IU/l, total bilirubin 1.50 mg/dl, direct bilirubin 0.14 mg/dl; prothrombin time and INR were normal.

The serological examinations revealed positivity for HBsAg and hepatitis B core antigen antibodies (Anti-HBcAg). Serum HBV-DNA was 26302748 IU/ml. The patient was diagnosed with HBV-related acute hepatitis. Given this situation, TMZ administration was interrupted. The patient underwent ultrasonography which showed only mild steatosis. Given the well known high risk of morbidity and mortality reported in this setting[6], considering the patient's need to continue anticancer treatment, the antiviral entecavir 0.5 mg/day was started to control HBV reactivation. Since dexamethasone administration was necessary to control brain edema, the dosage of entecavir was later increased to 1 mg/day to counteract the potential effect of glucocorticosteroids that may enhance viral replication, thus, favoring the possible development of resistant strains[7].

LFTs gradually improved and twenty days after the first entecavir administration HBV-DNA had decreased by more than 3 logs to 11,305 IU/ml. One month later, HBV-DNA titer was further decreased to 142 IU/ml. At this stage, the patient was evaluated by the oncologists, who decided to re-start TMZ administration at the initial dose of 300 mg/m^2 for 5 days/28 days, a lower dosage as compared to the standard dose of 400 mg/m^2. Dose reduction was justified both by the reactivation of HBV and a low platelet count secondary to chemotherapy.

The patient is currently alive under treatment with TMZ and entecavir administration led to a positive outcome since the latest LFTs were normal and HBV-DNA titer was < 20 IU/ml.

However, fourteen months after the diagnosis, despite a reduction in size of the main neoplastic lesion, new pathological nodules appeared, thus suggesting the progression of GBM.

Discussion

GBM is the most common and deadliest of malignant primary brain tumors. Surgery is the standard treatment, but usually it is difficult to achieve a complete cure of GBM by surgery alone. Therefore, chemoradiotherapy is primarily used as an adjuvant approach. If GBM is inoperable, chemoradiotherapy represents the only possible treatment.

TMZ is a cytotoxic alkylating agent administered orally and usually well tolerated. One of the most common side effects is its myelotoxicity, with a high frequency of grade 3-4 lymphocytopenia[8] observed in 79% of patients during concomitant radiotherapy[4,9]. Immunosuppression due to anticancer therapy can lead to HBV reactivation in patients with signs of HBV infection, mainly in those with hematological malignancies[10,11]. HBV reactivation in an IC is defined by the appearance of a significant viremia (> 20,000 IU/ml), while the presence of a significant viremia and aminotransferase levels above the upper normal value is defined as reactivation of hepatitis B[12].

Considering the high risk of HBV reactivation in immunocompromised patients, the viral screening before starting the treatment is very important. Guidelines to manage HBV positive immunosuppressed patients have been developed[12-14] and these recommend HBV screening for all patients before starting chemotherapy, although not all of the oncological associations support universal screening of all patients scheduled for chemotherapy[15].

HBV reactivation during GBM treatment with TMZ is a rare but severe occurrence. Up to now only four other cases have been reported in literature[3,6-18]. In addition to TMZ, corticosteroids have been used for the treatment of three of the four aforementioned patients, as well as in our case. When corticosteroids are used in combination with chemotherapy, it is not possible to exclude their potential role in HBV reac-

tivation. However, from the data available in the literature, the prolonged use of TMZ in GBM seems to play an independent role in the incidence of this complication.

Conclusions

Clinicians should be aware of this potential adverse event and, in order to avoid it, HBV screening must be performed before starting TMZ administration. Antiviral prophylaxis, if needed, can be provided according to existent guidelines.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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