Management of Cytomegalovirus Infection in a Patient with Malignant Glioma Treated with Temozolomide and Steroids

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Abstract

Temozolomide (TMZ) is the standard chemotherapy treatment for glioblastoma. Lymphocytopenia is reported to be the most frequent and severe adverse effect of TMZ and leads to opportunistic infections. Few cases of TMZ-induced cytomegalovirus (CMV) reactivation have so far been reported, and there are no guidelines regarding the use of chemotherapy after recovery from CMV reactivation. We herein report the case of a 45-year-old man with glioblastoma who developed CMV hepatitis following surgery and chemoradiotherapy with concomitant TMZ and steroids. After successful treatment of the CMV infection with an antiviral agent and recovery from the lymphocytopenia were achieved, the patient resumed maintenance therapy with TMZ under careful monitoring of his lymphocyte count and CMV pp65 antigenemia level.

Key words: cytomegalovirus, reactivation, temozolomide, immunosuppression, malignant glioma

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Introduction

Glioma patients are often treated with corticosteroids for prolonged periods to reduce intracranial swelling. Corticosteroids may lead to immunosuppression and vulnerability to opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (PCP), Cryptococcal meningoencephalitis and aspergillosis (1-3). Temozolomide (TMZ) is the standard therapeutic agent used to treat patients with malignant glioma (4). Severe adverse events such as leukopenia, anemia, thrombocytopenia, vomiting and nausea have been reported in patients who undergo TMZ therapy; however, unlike the adverse events associated with other chemotherapeutic agents previously used to treat malignant gliomas, the adverse events associated with TMZ are reversible and have rather low incidences (5). Severe lymphocytopenia induced by TMZ leads to opportunistic infections such as PCP (6, 7) and fulminant hepatitis due to reactivation of the hepatitis B virus (HBV) (8, 9). TMZ can also induce cytomegalovirus (CMV) reactivation (6, 10-14) due to lymphocytopenia and cause CMV pneumonia (11-14), colitis (6, 10, 12) and

transverse myelitis (6). No reports have yet investigated the resumption of chemotherapy after recovery from CMV reactivation. Prophylaxis for PCP with trimethoprim-sulfamethoxazole reduces the risk of infection, and trimethoprim-sulfamethoxazole treatment has been recommended since the first research studies of TMZ were performed (15). CMV seropositivity in the Japanese population is higher than that in Europeans, and the overall CMV seroprevalence of IgG has been reported to be 68.4% in Japanese puerperal women (16). However, the optimal management strategy for treating CMV infection and reactivation in patients with malignant glioma treated with TMZ who resume chemotherapy after recovery from CMV reactivation remains unclear because the number of reported cases is limited.

We herein report the case of a glioblastoma patient who developed severe lymphocytopenia, continuous fever and hepatitis following surgery and radiotherapy with concomitant TMZ and steroid treatment. After recovering from CMV reactivation, the patient continued maintenance therapy with TMZ for eight cycles under careful monitoring for CMV reactivation.

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Figure 1. A: Magnetic resonance images (MRIs) obtained before radiotherapy with concomitant temozolomide therapy showing a tumor in the right thalamus enhanced with gadolinium diethylenetriamine pentaacetic acid. B: MRIs obtained after chemoradiotherapy. The enhanced lesion in the right thalamus was smaller. C: MRIs obtained after three cycles of maintenance chemotherapy. The enhanced lesion in the right thalamus had diminished further in size. D: The recurrent tumor on MRI. The enhanced lesion extended to the right temporal lobe after eight cycles of maintenance chemotherapy.

Case Report

A 45-year-old man presented with a loss of appetite, memory disturbance and left hemiparesis. MRI showed hydrocephalus and a mass enhanced with gadolinium diethylenetriamine pentaacetic acid in the right thalamus extending to the right temporal lobe. Four days after undergoing surgery to place a ventriculoperitoneal shunt, the patient was transferred to our hospital for diagnosis and treatment. A histopathological examination of a biopsy specimen of the tumor in the right temporal lobe showed the tumor to be a glioblastoma. Chemoradiotherapy and concurrent TMZ were administered. Before chemoradiotherapy was initiated, the patient's white blood cell (WBC) count, absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were 6,400 cells/ μ L, 4,640 neutrophils/ μ L and 1,390 lymphocytes/ μ L, respectively. However, because the patient had elevated liver enzyme levels (AST: 43 IU/L; ALT: 164 IU/L), radiotherapy alone was initiated (Fig. 1A). Abdominal ultrasonography showed no abnormal findings; therefore, considering the possibility for the development of drug-induced hepatic disorder, treatment with valproic acid, trimethoprim-

sulfamethoxazole and famotidine was discontinued and the administration of prednisolone only was continued to treat brain edema. The hepatic transaminase levels eventually decreased, and TMZ administration (75 mg/ m^2 per day) was initiated 14 days after commencing radiotherapy. The patient completed radiotherapy (60 Gy/30 fr) and received concurrent TMZ (75 mg/ m^2 per day) for 33 days. The dose of prednisolone was gradually tapered from 15 mg/day during the administration of chemoradiotherapy and discontinued at the end of the chemoradiotherapy regimen. The total dose of prednisolone administered after the patient was transferred to our hospital was 1,145 mg for 60 days. After the chemoradiotherapy regimen was completed, a Common Terminology Criteria for Adverse Events v4.0 (CTCAE) grade 3 lymphocytopenia related to TMZ was observed (WBC count: 2,500 cells/ μ L; ANC: 1,880 neutrophils/ μ L; and ALC: 330 lymphocytes/ μ L). MRI showed that the tumor had decreased in size (Fig. 1B).

Three days after the radiotherapy with concurrent TMZ regimen was completed, the patient presented with fever ($\geq 38^\circ\text{C}$), nausea and elevated hepatic transaminase levels (AST: 125 IU/L; ALT: 329 IU/L). He did not complain of pulmonary or gastrointestinal symptoms such as cough and diarrhea. Abdominal ultrasonography showed no abnormal findings. The results for hepatitis B surface antigens, hepatitis B core antibodies, hepatitis C virus antibodies, hepatitis A virus antibody IgM and Epstein-Barr viral capsid antigen (VCA) IgM were all negative. The CMV IgM index was positive (1.49). Additionally, the CMV IgG index was positive (40.8) on the fourth day after the patient complained of fever and nausea. The CMV antigen test was positive for pp65 antigenemia (91 cells per 50,000 leukocytes) and a diagnosis of CMV reactivation was suspected due to the high IgG index. Initially, the elevated level of hepatic transaminase decreased gradually without medication administration. Consequently, we observed the patient's condition and ganciclovir was not administered. However, the patient continued to have a high fever every day, and the hepatic transaminase levels and number of CMV pp65 antigen-positive cells gradually increased (701 cells per 50,000 leukocytes). The patient's WBC count, ANC and ALC were 1,100 cells/ μ L, 860 neutrophils/ μ L and 60 lymphocytes/ μ L, respectively, and grade 4 lymphocytopenia was observed. Antibiotic therapy (meropenem) was initiated, considering the possibility for pneumonia; however, the patient continued to have a high fever every day and the levels of hepatic transaminase gradually increased (AST: 143 IU/L; ALT: 309 IU/L). The patient did not complain of pulmonary symptoms, colitis or urinary disease, and chest radiography did not show any abnormal findings. No source of the high fever was identified and CMV hepatitis was diagnosed. Antiviral (ganciclovir: 5 mg/kg twice a day) and antibiotic treatment (meropenem and pazufloxacin) was administered for 14 days. The patient's body temperature, hepatic transaminase levels and number of CMV pp65 antigen-positive cells (7 cells per 50,000 leukocytes) gradually decreased. Seventeen days af-

Figure 2. The clinical course of the patient with malignant glioma and CMV reactivation. Tumor resection was performed on day 0. RT: radiation therapy, TMZ: temozolomide, BT: body temperature, AST: aspartate aminotransferase, ALT: alanine aminotransferase, WBC: white blood cell, Ly: lymphocyte, Neu: neutrophil

ter initiating treatment with ganciclovir, the WBC count, ANC and ALC were 3,100 cells/ μ L, 1,640 neutrophils/ μ L and 680 lymphocytes/ μ L, respectively, and the number of CMV pp65 antigen-positive cells again increased (48 cells per 50,000 leukocytes). Ganciclovir (5 mg/kg twice a day) was administered for another 21 days until the number of CMV pp65 antigen-positive cells was zero. The patient's general condition showed an obvious clinical improvement and he was discharged 82 days after completing chemoradiotherapy.

Ninety-eight days after the chemoradiotherapy regimen was completed, the patient's blood count was normal (WBC count: 7,150 cells/ μ L; ANC: 4,075 neutrophils/ μ L; ALC: 1,430 lymphocytes/ μ L), the CMV pp65 antigen test results were negative and the patient started the first cycle of maintenance TMZ therapy. Reduced doses (100 mg/ m^2) were administered to prevent CMV reactivation. No complications occurred and the patient received the second cycle of TMZ (150 mg/ m^2). The dose was increased up to 200 mg/ m^2 after three cycles (Fig. 1C). Eight cycles of TMZ maintenance therapy were administered without any complications (minimum ALC: 620 lymphocytes/ μ L). After the eight cycles of TMZ were completed, MRI showed tumor progression (Fig. 1D). Chemotherapy was discontinued and the patient

received palliative care for his malignant disease. His clinical course is presented in Fig. 2.

Discussion

TMZ is the standard therapeutic agent for treating patients with malignant glioma (4). TMZ causes immunosuppression leading to the development of opportunistic infections such as PCP and hepatitis B (8, 9). This characteristic immunosuppression can also induce CMV reactivation, a rare complication (6, 10-14). The incidence of TMZ-induced CMV reactivation, its risk factors and its optimal management remain unclear. Steroids also cause immunosuppression, and the majority of reported cases of opportunistic CMV infection, including the present case, have occurred when patients were treated with concurrent TMZ and steroids (6, 10-14). Therefore, treatment with TMZ in combination with steroids is believed to cause immunosuppression and subsequent CMV reactivation. All previous cases of CMV reactivation associated with TMZ therapy involved lymphocytopenia (ALC range: 0-703 lymphocytes/ μ L) (6, 10-14). Our patient also presented with severe lymphocytopenia (ALC: 60 lymphocytes/ μ L). Some reports have shown that CD4+ T-lymphocyte counts are less than 260/ μ L in CMV patients

who are treated with TMZ (10, 12). Narrow monitoring of the lymphocyte and CD4+ T-lymphocyte counts is recommended in patients receiving TMZ and steroids. Physicians should be aware of the possibility for CMV reactivation when the ALC or CD4+ T-lymphocyte count of a patient treated with concurrent TMZ and steroids decreases to approximately 500 lymphocytes/ μ L (grade 3/4 lymphocytopenia) or 300/ μ L, respectively (6, 10-14).

CMV generally causes self-limited, mild and asymptomatic infections in immunocompetent patients. Some of these patients develop infectious mononucleosis or glandular fever-like syndrome (17) with a prolonged fever and mild hepatitis. Our patient also had a continuous high fever, elevated hepatic transaminase levels and loss of appetite. We investigated the causes of the fever and hepatitis, including possible drug reactions. We did not find any source of the high fever, and we diagnosed CMV reactivation-induced hepatitis. The patient's condition gradually improved after ganciclovir treatment was initiated. However, after 17 days of ganciclovir treatment, the ALC remained at 680 lymphocytes/ μ L and the number of CMV pp65 antigen-positive cells again increased. This suggests that CMV infections recur during severe lymphocytopenia. There is no obvious consensus regarding the most effective prophylaxis for CMV infection in glioma patients treated with TMZ, and the optimal management strategy for CMV reactivation under chemotherapy remains unclear. Current opinion is that CMV infection in immunocompetent patients does not require treatment; however, the risks and benefits of specific antiviral treatments for severely ill patients have not yet been adequately evaluated. Antiviral treatment for CMV infection should continue until confirmation of negative test results for CMV pp65 antigenemia is received or the patient recovers from severe lymphocytopenia. Developing guidelines for the management of CMV reactivation under chemotherapy is necessary.

In this case report, we discussed the safety of continued TMZ maintenance therapy administered after CMV reactivation. The patient received eight cycles of TMZ maintenance therapy without developing complications after confirming his recovery from lymphocytopenia and CMV pp65 antigenemia. The tumor was controlled for 12.5 months after the initial treatment was administered.

CMV seropositivity in the Japanese population is higher than that in Europeans, and the overall CMV seroprevalence of IgG has been reported to be 68.4% in Japanese puerperal women (16). The rate of CMV antibody carriers in Asia and Africa is 90% to 100% higher than that in Western countries (40-50%) (18). It is therefore necessary to be aware of the possibility for CMV reactivation in Japanese and Asian immunocompromised cancer patients.

In conclusion, because CMV reactivation and infection is a fatal adverse effect of TMZ, physicians should be alerted to the possibility for CMV reactivation when unexplained symptoms are found in patients treated with TMZ. CMV reactivation occurs more frequently in patients treated with

TMZ, especially in combination with steroids. Antiviral treatment is effective; however, when CMV infection is suspected, cautious monitoring of clinical symptoms, lymphocyte counts and the CMV pp65 antigenemia levels is necessary during continued TMZ treatment in glioma patients.

The authors state that they have no Conflict of Interest (COI).

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