CASE REPORT

Reactivation of cytomegalovirus following treatment of malignant glioma with temozolomide

**Yoshiko Okita · Yoshitaka Narita · Yasuji Miyakita ·
Makoto Ohno · Kohki Aihara · Shinichiro Mori ·
Takamasa Kayama · Soichiro Shibui**

Abstract Temozolomide is a standard chemotherapeutic agent in the treatment of malignant gliomas. Lymphocytopenia is reported to be the most frequent and severe adverse effect, which causes opportunistic infections such as pneumocystis pneumonia (PCP) and increases the risk of the reactivation of viruses such as hepatitis B virus (HBV) and cytomegalovirus (CMV). However, the incidence of temozolomide-induced CMV reactivation remains unclear. We report on a case of a 62-year-old female with gliomatosis cerebri who had severe lymphocytopenia and pneumonia following concurrent temozolomide treatment and prophylaxis for PCP. She presented cough, fever, and severe lymphocytopenia 1 month after chemoradiotherapy with temozolomide. Her serum β-D-glucan levels remained within the normal range, which was helpful to rule out a diagnosis of PCP. Other opportunistic infections were ruled out, and a blood test for the CMV antigen was positive for pp65 antigenemia. The patient was diagnosed as having CMV pneumonia. She was treated with ganciclovir and recovered. It was very difficult to distinguish between PCP and CMV pneumonia with only the clinical presentation and radiological findings. When a patient receives temozolomide, it is important to be aware of the potential for a CMV reactivation. The serum β-D-glucan levels and pp65 antigenemia are very useful for diagnosis of CMV pneumonia.

Introduction

Temozolomide is the standard therapy for patients with malignant glioma [1]. The incidence of severe adverse events, such as leukopenia, anemia, and thrombocytopenia, as well as vomiting or nausea, has been reported to be rather low and reversible, compared with other chemotherapeutic agents previously used for malignant gliomas [2]. However, severe lymphocytopenia induced by temozolomide causes opportunistic infections, such as pneumocystis pneumonia (PCP) [3, 4] or fulminant hepatitis due to the reactivation of the HBV [5]. Temozolomide has also been reported to induce CMV reactivation [4, 6–9], which is due to lymphocytopenia, and to cause CMV pneumonia [6–8], colitis [4, 7, 9], and transverse myelitis [4].

We herein report on the case of a patient with severe lymphocytopenia and CMV pneumonia following temozolomide treatment.

Case report

A 62-year-old woman with gliomatosis cerebri was admitted with pneumonia. Initially, she presented with dementia and scored 20 points on the Mini-Mental State Examination. She was diagnosed with gliomatosis cerebri in both frontal to left temporoparietal lobes on the basis of magnetic resonance (MR) images (Fig. 1a). The tumor was biopsied from the left frontal lobe, and the pathological diagnosis was diffuse astrocytoma, grade 2. She was treated with temozolomide alone because the irradiation field

Y. Okita · Y. Narita (✉) · Y. Miyakita · M. Ohno ·
K. Aihara · T. Kayama · S. Shibui
Department of Neurosurgery and Neuro-Oncology,
National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku,
Tokyo 104-0045, Japan
e-mail: yonarita@ncc.go.jp

S. Mori
Department of Stem Cell Transplantation, National Cancer
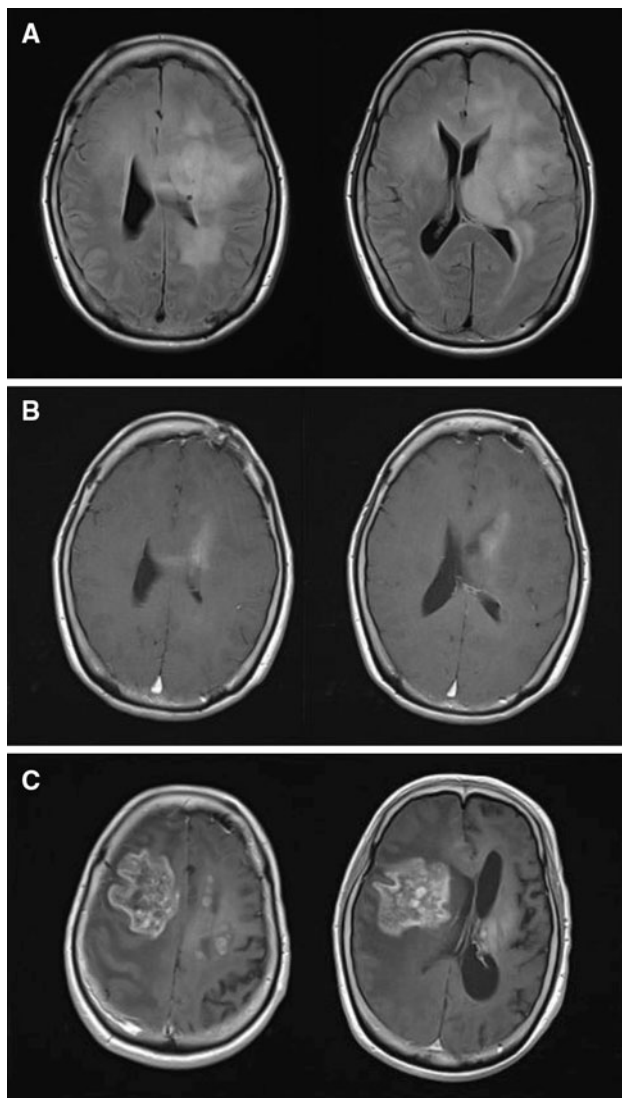Center Hospital, Tokyo, Japan

Fig. 1 a Preoperative MR images: tumor in the bilateral frontal to left temporoparietal lobes in the fluid-attenuated inversion recovery (FLAIR) image. b MR images of first recurrence: newly enhanced lesion in the bilateral frontal lobes involving the corpus callosum. c MR images of second recurrence: newly developed ring-enhancing lesions with tumor recurrence in the bilateral frontal lobes

was very large and extended from the left dominant hemisphere to the right frontal lobe and because there was a possibility of radiation-induced cognitive dysfunction. She underwent chemotherapy with temozolomide (150 mg/m^2 per day) for the first 5 days of a 28-day cycle, and continued temozolomide treatment (200 mg/m^2) almost every 4 weeks. After 6 cycles of temozolomide, she presented with global aphasia and the inability to walk. MR imaging showed a mass that was slightly enhanced with gadolinium diethylenetriamine pentaacetic acid in the left frontal lobe that was not seen before the initial treatment (Fig. 1b). She was diagnosed with recurrence and malignant change from grade 2 astrocytoma, and she underwent

and completed radiotherapy (54 Gy in 30 fractions) and concurrent temozolomide (75 mg/m^2 per day) treatment for 42 days. She was given 20 mg/day predonisolone, and her neurological symptoms recovered slightly. At the same time, she took cotrimoxazole (trimethoprim–sulfamethoxazole 1 g/day) for prophylaxis against PCP. Before chemoradiation therapy was started, her white blood cell (WBC) count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) were 6,300 cells/μL, 5,390 neutrophils/μL, and 570 lymphocytes/μL, respectively. In addition, the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) for grade 2 lymphocytopenia related to TMZ were observed. After the chemoradiation therapy, the lymphocytopenia worsened to grade 4 (WBC count 2,300 cells/μL, ANC 2,160 neutrophils/μL, and ALC 80 lymphocytes/μL), and she was discharged without any respiratory symptoms and was followed up with predonisolone (20 mg/day). She continued to take cotrimoxazole for prophylaxis. Total administered dose of TMZ after chemoradiation therapy was 12,800 mg. Two weeks after completion of the chemoradiation therapy, her ALC recovered slightly (220 lymphocytes/μL), but the grade 3 lymphocytopenia persisted. One month after the completion of the radiotherapy and temozolomide treatment, she experienced cough, fever, and dyspnea, and she was readmitted to our hospital.

At admission, her WBC count, ANC, and ALC were 4,500/μL, 4,370/μL, and 0/μL, respectively, and grade 4 lymphocytopenia was observed. Radiography (Fig. 2b) and a high-resolution computed tomography (CT) scan of the chest (Fig. 2c) were performed, which revealed interstitial pneumonitis with diffuse bilateral interstitial infiltrations. After consulting the chief of the infection control team (ICT), she was treated with the antibiotics cefazolin (CEZ) and azithromycin (AZM). The serum β-D-glucan levels remained within the normal range (8.3 pg/mL). We checked sputum and blood culture, the influenza virus antigen, the urinary antigen of *Legionella*, and screened for the Epstein–Barr virus, but those examinations were negative for the cause of pneumonia. Because the patient took cotrimoxazole as prophylaxis for PCP during and after chemoradiation therapy, CMV pneumonia was highly suspected (Fig. 3). A blood sample was obtained in order to test for the CMV antigen, and it was positive for pp65 antigenemia (329 cells per 43,000 leukocytes). It was difficult to diagnose PCP or CMV pneumonia on the basis of the CT radiological findings. She was diagnosed as having CMV pneumonia because other opportunistic infections were ruled out, and the blood test for the CMV antigen was positive for pp65 antigenemia. She started to receive ganciclovir together with antibiotics including CEZ, AZM, and cefmetazole (CMZ), and the predonisolone was gradually tapered. The intravenous ganciclovir dosage was 5 mg/kg

Fig. 2 a Chest radiograph before biopsy on first admission. **b** Pretreatment chest radiograph. **c** Pretreatment chest CT; interstitial pneumonitis with diffuse bilateral interstitial infiltrates was verified. **d** Post-treatment chest radiograph showing improvement of interstitial pneumonitis
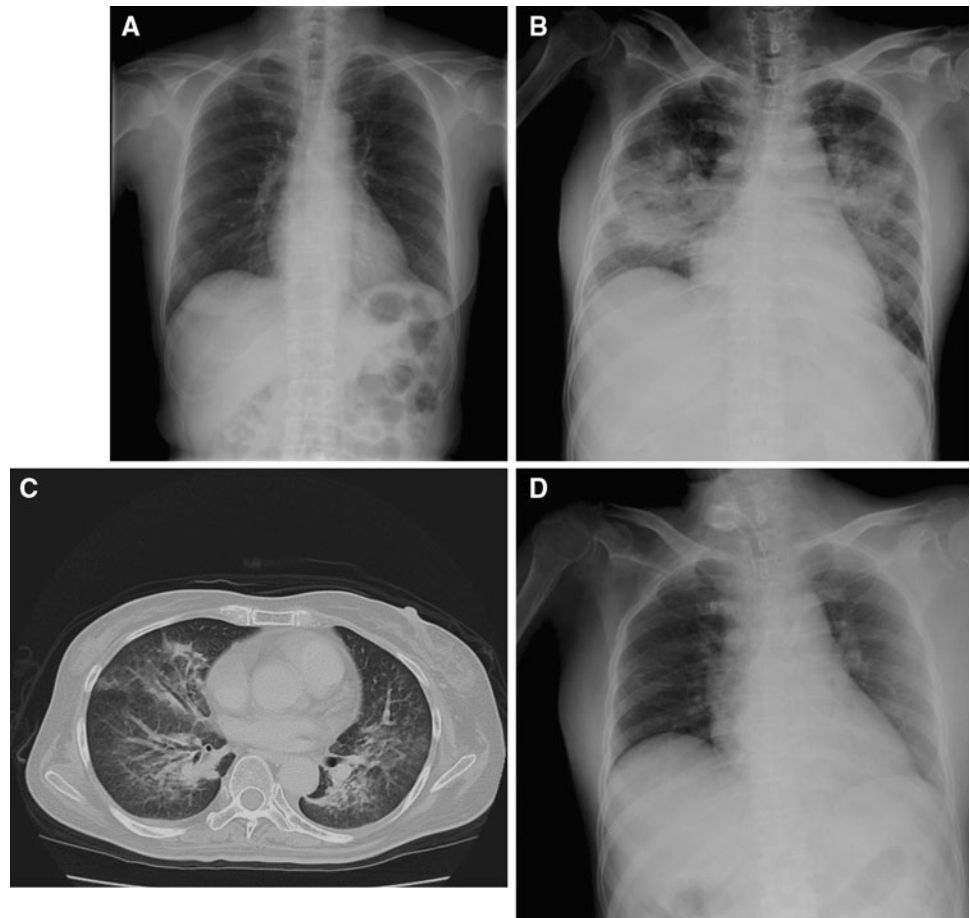
twice a day for 14 days. Furthermore, the frequency of intravenous ganciclovir was decreased once a day for next 12 days. She became afebrile about 1 week after the treatment with ganciclovir. After receiving ganciclovir for 20 days and antibiotics for 23 days, the test for the CMV pp65 antigen was negative and her respiratory state recovered gradually (Fig. 2d). Five months after completion of the chemoradiation therapy, MR imaging showed tumor progression (Fig. 1c), and she became bedridden. She was eventually transferred to another hospital for palliative treatment of her malignant disease.

Discussion

Temozolomide is the standard therapy for patients with malignant glioma [1]. The total incidence and incidence of grade 3/4 leukopenia were 38 and 3%, those of neutropenia were 47 and 6%, those of lymphocytopenia were 50 and 25%, and those of thrombocytopenia were 31 and 9% in another clinical study conducted in Japan [10]. At our institution, grade 3/4 lymphocytopenia occurred in 40% of the patients just after radiotherapy with concurrent temozolomide treatment and in 20% of the patients after 6

cycles of adjuvant temozolomide chemotherapy (data not shown). Because temozolomide is associated with CD4$^+$ T-cell dysfunction, treatment with temozolomide is possibly associated with a decline of the immune system and an increased susceptibility to opportunistic infections such as PCP [3, 4]. This characteristic immunosuppression also induces CMV reactivation as a rare complication [4, 6–9]. The incidence and risk factors of temozolomide-induced CMV reactivation, as well as its optimal management, remain unclear. Steroids also causes immunosuppression and the majority of reported cases of opportunistic CMV infection occurred when patients were treated concurrently with temozolomide and steroids [4, 6–9], including our case. Therefore, treatment with temozolomide in combination with steroids is supposed to be the cause of immunosuppression and subsequent CMV reactivation.

It was reported that 2.9% of adults with leukemia were diagnosed with CMV pneumonia [11]. CMV reactivation due to severe lymphocytopenia has been reported to occur in only 0.3% of patients with solid tumors such as lung and breast cancers who received docetaxel-based chemotherapy [12]. The risk of infection is increased with the use of T-lymphocytotoxic chemotherapies, e.g., cytarabine, fludarabine, or high-dose cyclophosphamide and
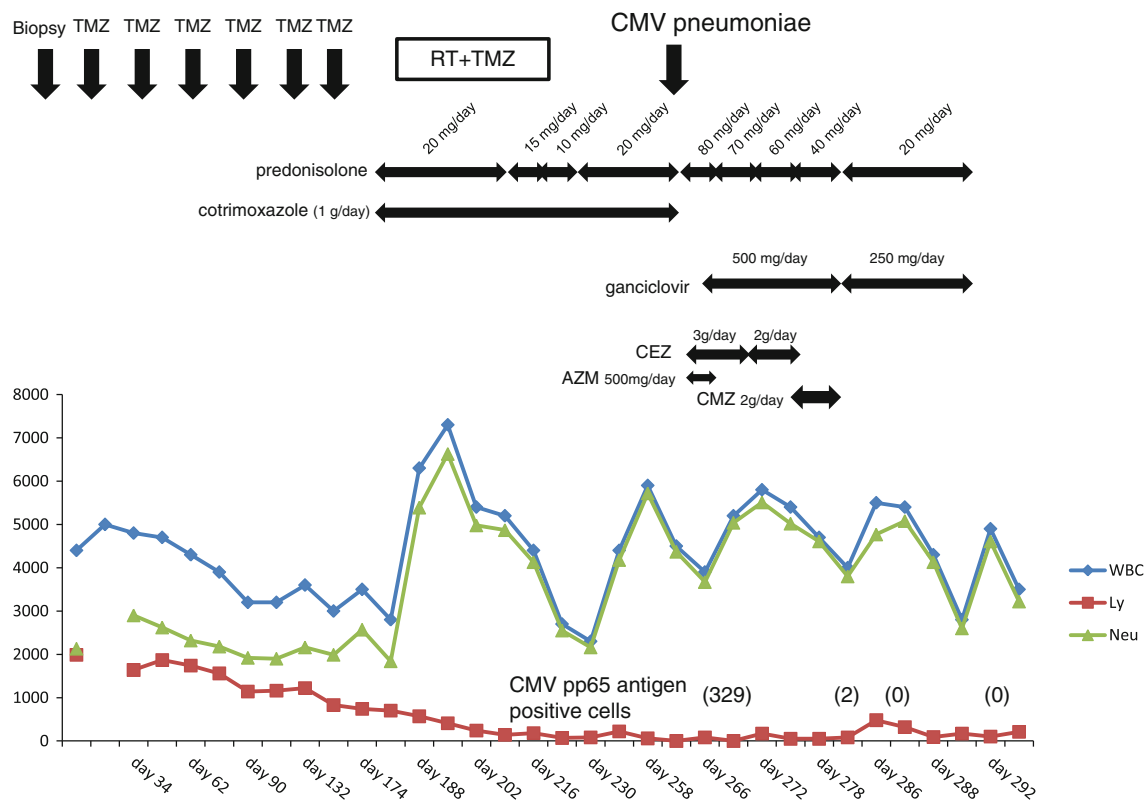
Fig. 3 Clinical course of malignant glioma patient with CMV pneumoniae. Biopsy was performed at day 0. *RT* radiation therapy, *TMZ* temozolomide, *WBC* white blood cell, *Ly* lymphocyte, *Neu* neutrophil, *CEZ* cefazolin, *AZM* azithromycin, *CMZ* cefmetazole

with the use of T-cell suppressors, e.g., methotrexate or corticosteroids [13].

The clinical presentation of both PCP and CMV pneumonia consists of fever, dyspnea, and unproductive cough and the radiological differentiation of CMV pneumonia and PCP is usually difficult even by thin-section CT scans [14–16]. Prophylaxis for PCP with cotrimoxazole has been recommended since the first research studies were performed with temozolomide [17]. According to Green et al. [18], prophylactic cotrimoxazole was highly effective in preventing PCP infection, and the treatment lowered the incidence of PCP infection by 91%. Even when grade 3/4 lymphocytopenia is observed, it seems that patients treated with temozolomide and prophylactic cotrimoxazole are at low risk of developing PCP. At our institution, patients receiving more than 15 mg/day of predonisolone or those with grade 3/4 lymphocytopenia received cotrimoxazole (1 g/day) as prophylaxis for PCP. Previously, three cases of CMV pneumonia that were induced by temozolomide were reported, and lymphocytopenia occurred in all of them [6–8]. Two of them experienced only CMV pneumonia, and prophylaxis for PCP with cotrimoxazole had been provided for one of them [7], whereas cotrimoxazole was not mentioned for the other case [6]. The third case reported by Douzinas et al. [8] was not offered cotrimoxazole and

developed severe PCP and coexisting CMV pneumonia. Furthermore, Vogel et al. [16] reported that 84% of patients who were diagnosed with CMV pneumonia had received PCP prophylaxis. However, none of the patients who were diagnosed with PCP received PCP prophylaxis.

In previous reports, screening for a CMV infection by means of antigenemia or CMV polymerase chain reaction assays was carried out, and these methods correlated with disease identification [6–9]. Tasaka et al. [19] reported that serum β-D-glucan levels were significantly higher in PCP-positive patients than in PCP-negative patients ($p < 0.0001$). They showed that the sensitivity, specificity, and negative predictive value of β-D-glucan levels were 92.3, 86.1, and 98.0%, respectively, and the cutoff level of β-D-glucan was estimated to be 31.1 pg/mL [19]. Other reports describing temozolomide-induced CMV pneumonia so far have not reported the levels of β-D-glucan [4, 6–9]. Normal serum β-D-glucan level and pp65 antigenemia were very useful for diagnosis of CMV pneumonia in our case.

According to a report in 1973 [20], the rate of CMV antibody carriers in Japan was 96% and those in Asia and Africa were 90–100%, both higher than that in Western countries (40–50%). The rate of CMV antibody carriers among pregnant women in Japan decreased gradually from 93.2% in 1980 to 66.7% in 1995 [21] but it is still high. It is

important to be aware of the potential for CMV reactivation during treatment with temozolomide and steroids, particularly in Asian and African countries.

Conflict of interest   We declare that there are no conflict of interest.

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