Epstein-barr Virus Negative Primary Central Nervous System Lymphoma Developed after Treatment of Glioblastoma: A Case Report

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Abstract

Temozolomide is an oral alkylating agent with moderate side effects compared to other agents. However, the development of secondary malignancies following temozolomide has been reported. We describe the first case of primary central nervous system lymphoma (PCNSL) occurrence following glioblastoma treatment. A 69-year-old male was admitted to our hospital with a chief complaint of headache and dysnomia for six months. A ring-enhanced mass of the left temporal lobe was observed and gross total removal was performed. The tumor was pathologically diagnosed as isocitrate dehydrogenase (IDH)-wildtype glioblastoma and he received 60 Gy of local irradiation in 30 fractions, with concurrent temozolomide at a dose of 75 mg/m2. Grade 2 lymphopenia was discovered during treatment. Within 6 months, the patient developed a right parietal intra-axial tumor without local recurrence and was given 150-200 mg/m2 oral temozolomide for five consecutive days of a 28-day cycle. Within five cycles of temozolomide, complete remission was observed; however, after the eighth cycle, a new lesion in the right temporal lobe was discovered. Surgical removal was performed and histological findings were consistent with diffuse large B-cell lymphoma, and the final diagnosis of Epstein-Barr virus negative PCNSL was established.

Keywords: Glioblastoma, Diffuse large B-cell lymphoma, Primary central nervous system lymphoma, Temozolomide

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive malignant brain tumor in adults. Despite extensive research on its potential therapy, the survival rate of patients with GBM remains low with a median survival rate of 12-15 months since the diagnosis was established. Current standard treatment for GBM involves the combination of surgical resection, followed by concomitant radiotherapy and temozolomide, and adjuvant temozolomide. Temozolomide is an oral second-generation alkylating agent that is primarily used in treating glioblastoma and is known to improve the median survival rate to 2.5 months compared to radiotherapy alone.1 While temozolomide is deemed essential in treating glioblastoma, temozolomide-related adverse events are well reported, including the development of secondary malignancies.2

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive, and prognostically poor extranodal non-Hodgkin’s lymphoma confined to the central nervous system with a low propensity for systemic dissemination.3 Current treatment strategies consist of systemic chemotherapy with or without whole brain radiotherapy. Albeit PCNSL is radio and chemotherapy-sensitive, remission is frequently short-lasting, therefore leading to recurrence and additional chemotherapy.4

The case report aims to share our experience with the development of PCNSL following glioblastoma treatment.
To our best knowledge, there has been no report of Epstein-Barr virus (EBV) negative PCNSL development after treatment for glioblastoma.

**Case Report**

A 69-year-old male suffered progressive headache and dysnomia 6 months ago. He was under the administration of an antihypertensive drug against hypertension and had regular magnetic resonance imaging (MRI) follow-up for his left vestibular schwannoma which was diagnosed solely by imaging. On admission, his score on the mini-mental state examination and revised version of Hasegawa’s Dementia Scale were 27 and 20, respectively. Visual field examination revealed the right superior quadrantanopia. Imaging studies revealed a ring-enhanced mass at the left temporal lobe with perifocal brain edema (Fig. 1A-E) and the left vestibular schwannoma (Fig. 1F). He underwent awake surgery and gross total removal of the enhanced tumor was achieved. Hematoxylin & eosin (H.E.) staining showed a diffuse proliferating tumor and moderately pleomorphic nuclei hyperchromatism and atypical mitosis with endothelial proliferation and palisading necrosis (Fig. 1G). Immunohistochemically, these tumor cells were markedly reactive to GFAP (Fig. 1H), OLIG2, and negative for IDH1R 132H and Synaptophysin. The MIB-1 labeling index was a maximum of 10% in the hot spot area, and the histological diagnosis was glioblastoma, IDH-wildtype. He underwent 60 Gy of local irradiation in 30 fractions, with concurrent temozolomide at a dose of 75 mg/m$^2$. Grade 2 lymphopenia was observed during treatment. The patient reported a change of mood and refused the suggested adjuvant treatment with temozolomide.

He developed a right parietal intra-axial tumor 6 months after local irradiation with concurrent temozolomide (Fig. 2A-E) without local recurrence (Fig. 2F). The imaging diagnosis at this point was a distant recurrence of glioblastoma, and he was administered 150-200 mg/m$^2$/day of oral temozolomide for 5 days during the 28-day cycle. The MRI findings after five cycles of temozolomide revealed complete remission of the right parietal tumor. However, at the eighth cycle of temozolomide, he developed a right temporal lobe tumor (Fig. 3A-E) without recurrence of both the left temporal and right parietal tumor (Fig. 3F). He underwent surgical removal of the tumor and gross total removal was achieved. The H.E. staining showed diffuse proliferation of large atypical lymphocytes with hyperchromatic nuclei and scant cytoplasm (Fig. 3G). Immunohistochemically, these lymphoma cells were positive for leukocyte common antigen (LCA), CD20 (Fig. 3H),
CD79a, bcl-6, multiple myeloma oncogene-1 (MUM-1), bcl-2 (partly), and negative for CD3, CD5, CD10, c-Myc. The MIB-1 labeling index was >95%. These histological findings were consistent with diffuse large B-cell lymphoma, non-germinal center B-cell type. The EBV-encoded small RNA in situ hybridization (EBER-ISH) confirmed the negativity of EBV infection (Fig. 3I). He underwent a 18F-fluorodeoxyglucose-positron emission tomography and no extracranial lesion was detected. His final diagnosis was PCNSL. Imaging characteristics of the right parietal tumor were not the same as the left temporal glioblastoma but fairly similar to right temporal PCNSL imaging findings. Due to the previous 60 Gy of irradiation at the left temporal lobe, we were concerned about the development of leukencephalopathy following administration of HD-MTX, therefore, we decided to perform three cycles of carboplatin-etoposide treatment. He was transferred to another hospital and passed away 11.5 months after his last chemotherapy treatment because of a recurrence of PCNSL.

**Discussion**

Even though the side effects from temozolomide are more modest than other alkylating agents, several studies have reported the development of secondary malignancies following glioblastoma treatment, such as squamous cell carcinoma, basal cell carcinoma, prostate cancer, breast cancer, and extracranial non-Hodgkin’s lymphoma. However, there was only one report of the development of intracranial non-Hodgkin’s lymphoma, and this is the first report of EBV-negative PCNSL development after treatment with temozolomide for glioblastoma. The overall survival of patients with glioblastoma is usually short, which might be the reason for the very low incidence of development with non-Hodgkin’s lymphoma in glioblastoma patients.

The PCNSL is a rare type of extranodal non-Hodgkin’s lymphoma that is typically found in the brain, spinal cord, cerebrospinal fluid, or eyes. Diffuse large B-cell lymphoma accounts for approximately 90% of PCNSL, while the remaining 10% is contributed to low-grade B-cell lymphoma, Burkitt’s lymphoma, or T-cell lymphomas. Most PCNSLs develop mainly in immunocompetent patients, but PCNSL
develops at a higher incidence in immunosuppressive patients (e.g., under the administration of immunosuppressive agents or HIV/AIDS). It has been estimated that overall PCNSL after immunosuppression accounts for <10% of PCNSL cases (<0.1% of NHL). The increased incidence of post-transplantation lymphoproliferative disorder (PTLD) and PCNSL are concordant with the rising case numbers of solid organ transplantation and allogenic hematopoietic stem cells, which are significantly related to morbidity and mortality. An EBV has also been strongly linked with the occurrence of PTLD/PCNSL in immunocompromised patients, with EBV genomic materials detected in >90% PCNSL tissue. However, the EBV virus was not detected in our case.

The PCNSL recurrence occurs in approximately 36%-66.6% of patients following initial treatment, with the first relapse primarily occurring within 2 years after the initial diagnosis. There are many factors related to PCNSL recurrences, including age more than 60 years old, intraocular involvement, and initial treatment. For the first relapse, the vast majority of cases occurred within the central nervous system. Approximately >50% of relapsed PCNSL involves the brain and at a certain distance from the initial lesion.

Temozolomide is the most widely used chemotherapy in glioblastoma and strong evidence suggests that temozolomide administration provides survival benefits for patients with primary malignant diffuse gliomas. The O6-methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme that protects cells from the cytotoxic activity of temozolomide. However, bone marrow is highly susceptible to temozolomide due to the lower activity of MGMT which may lead to the development of myelosuppression and myelodysplastic syndrome. According to the study by Park et al., secondary hematological malignancy occurred frequently with a cumulative dose of 18,000 mg/m² and within 19 months of treatment duration. It is well-known that temozolomide causes lymphopenia as part of myelotoxicity, and previous research indicates that the incidence of severe lymphopenia was 31.6% and that treatment-related lymphopenia is strongly correlated with poor overall survival, low response rate, and recurrences. Furthermore, lymphopenia was reported to be a biomarker of impaired host immunity and a decreased low absolute lymphocyte count was a poor prognostic factor for patients with lymphoma and other cancers. Thus, we postulate that lymphopenia might cause mild immunosuppressive status in our case, which might result in the development of non-Hodgkin's lymphoma.

The development of cancer following radiation and chemotherapy has been well reported and evidence suggests a correlation between radiotherapy and secondary malign-
nancy in childhood cancer and young adult cancer. In addition, the emergence of secondary malignancies following glioblastoma treatment also has been frequently reported. A study involving 24,348 GBM patients from the Surveillance, Epidemiology and End Results (SEER) database revealed that the elderly had the highest incidence of second malignancies and the lowest overall survival compared to the pediatric and young populations. Furthermore, elderly patients had the shortest time to develop secondary malignancy (4.93 ± 11.68 months, P < 0.001) than other populations.  

The effectiveness of additional temozolomide in PCNSL is the subject of ongoing debate. As a result of a randomized Phase I and II study (RTOG0227) in which patients received methotrexate, temozolomide, and rituximab followed by WBRT consolidation, 51% of patients achieved complete response and 34% achieved partial response. In addition, CALGB50202 Phase II trials were revealed to offer a better prognosis compared to single chemotherapy alone. Nonetheless, some studies are not compliant with these findings. A randomized Phase II study revealed that the combination of high-dose methotrexate and temozolomide is associated with shorter overall survival compared to methotrexate, procarbazine, vincristine, and cytarabine group. 

A randomized Phase III failed to demonstrate the benefit of the addition of temozolomide to whole brain radiotherapy and adjuvant temozolomide after administration of high-dose methotrexate in newly diagnosed PCNSL. These findings implied that further studies of additional temozolomide in multidrug chemotherapy are mandatory.

The emergence of additional primary malignancies following temozolomide requires clinical and medical attention. Furthermore, PCNSL and glioblastoma could have similar characteristics, and establishing the diagnosis of PCNSL solely from imaging is sometimes challenging. In addition to the fact that this patient was diagnosed with left temporal glioblastoma, and the fact that both PCNSL and glioblastoma share similar imaging characteristics, led us to initially diagnose the right parietal tumor with distant glioblastoma recurrence and the decision to administer temozolomide. However, imaging characteristics of the right parietal tumor differed from the left temporal glioblastoma, but were fairly similar to right temporal PCNSL imaging findings, indicating that this lesion is most likely a PCNSL. Therefore, we emphasize the importance of surgical biopsy if the recent imaging findings are not in concordance with the initial findings. Future studies are also necessary to confirm the risk of temozolomide for the development of non-Hodgkin’s lymphoma.

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Informed Consent

Informed consent was obtained from the patient.

Conflicts of Interest Disclosure

There is no conflict of interest to declare

References

1) Stupp R, Mason WP, van den Bent MJ, et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352: 987-996, 2005
2) Kim JY, Jackman JG, Woodring S, et al.: Second primary cancers in long-term survivors of glioblastoma. Neurooncol Pract 6: 386-391, 2019
3) Grommes C, Deangelis LM: Primary CNS lymphoma. J Clin Oncol 35: 2410-2418, 2017
4) Shao L, Xu C, Wu H, et al.: Recent progress on primary central nervous system lymphoma-from bench to bedside. Front Oncol 11: 689843, 2021
5) Van Ginderachter L, Cox T, Drijkoningen R, et al.: Non-hodgkin lymphoma after treatment with extended dosing temozolomide and radiotherapy for a glioblastoma: a case report. Case Rep Oncol 6: 45-49, 2013
6) Sharma A, Gupta D, Mohanti BK, et al.: Non-hodgkin lymphoma following temozolomide. Pediatr Blood Cancer 53: 661-662, 2009
7) Zakaria Z, Fenton E, Khalil A, Sattar MT, Molnar P; Stupp-treated glioblastoma accompanied by EBV-positive primary CNS lymphoma. Br J Neurosurg 28: 287-289, 2014
8) Evens AM, David KA, Helenowski I, et al.: Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol 28: 1038-1046, 2010
9) Evens AM, Choquet S, Kroll-Desrosiers AR, et al.: Primary CNS posttransplant lymphoproliferative disease (PTLD): an international report of 84 cases in the modern era. Am J Transplant 13: 1512-1522, 2013
10) Allen UD, Preiksaitis JK, AST Infectious Diseases Community of Practice: Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 33: 1-22, 2019
11) Tao K, Wang X, Tian X: Relapsed primary central nervous system lymphoma: current advances. Front Oncol 11: 649789, 2021
12) Tabouret E, Houillier C, Martin-Duverneuil N, et al.: Patterns of response and relapse in primary CNS lymphomas after first-line chemotherapy: imaging analysis of the ANOCEF-GOELAMS prospective randomized trial. Neuro Oncol 19: 422-429, 2017
13) Gerson SL: Clinical relevance of MGMT in the treatment of cancer. J Clin Oncol 20: 2388-2399, 2002
14) Park R, Amin M, Trikalinos NA: Temozolomide duration and secondary hematologic neoplasms: a literature review and implications for patients with neuroendocrine neoplasms. J Neuroendocrinol 34: e13178, 2022
15) Zhang Y, Chen S, Chen H, et al.: prognostic value and risk factors of treatment-related lymphopenia in malignant glioma patients treated with chemoradiotherapy: a systematic review and meta-analysis. Front Neurol 12: 1-12, 2022
16) Grossman SA, Ellsworth S, Campian J, et al.: Survival in patients
with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. *J Natl Compr Cancer Netw* 13: 1225-1231, 2015

17) Jang JE, Kim YB, Kim SJ, et al.: A new prognostic model using absolute lymphocyte count in patients with primary central nervous system lymphoma. *Eur J Cancer* 57: 127-135, 2016

18) Li X, Li Y, Cao Y, et al.: Risk of subsequent cancer among pediatric, adult and elderly patients following a primary diagnosis of glioblastoma multiforme: a population-based study of the SEER database. *Int J Neurosci* 127: 1005-1011, 2017

19) Glass J, Won M, Schultz CJ, et al.: Phase I and II study of induction chemotherapy with methotrexate, rituximab, and temozolomide, followed by whole-brain radiotherapy and postirradiation temozolomide for primary CNS lymphoma: NRG oncology RTOG 0227. *J Clin Oncol* 34: 1620-1625, 2016

20) Rubenstein JL, Hsi ED, Johnson JL, et al.: Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol* 31: 3061-3068, 2013

21) Omuro A, Chinot O, Taillandier L, et al.: Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. *Lancet Haematol* 2: e251-e259, 2015

22) Mishima K, Nishikawa R, Narita Y, et al.: Randomized phase III study of high-dose methotrexate and whole brain radiotherapy with or without concomitant and adjuvant temozolomide in patients with newly diagnosed primary central nervous system lymphoma: JCOG1114C. *J Clin Oncol* 38: 2500, 2020

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