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Clinical/Scientific Notes

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PLASMABLASTIC LYMPHOMA AFTER STANDARD-DOSE TEMOZOLOMIDE FOR NEWLY DIAGNOSED GLIOBLASTOMA

Secondary malignancies due to alkylating agents or topoisomerase II inhibitors are a concern in patients treated for primary brain tumors of the nervous system. Myelosuppression is the dose-limiting toxic effect of the alkylating agent temozolomide; reversible hematologic toxicity consisting mainly of thrombocytopenia is reported to occur in 7% of patients treated with concomitant radiotherapy and temozolomide and 14% with adjuvant temozolomide.[1] However, the incidence of secondary malignancies and nonreversible hematologic disorders, such as myelodysplastic syndrome, are a rare complication of temozolomide.[2]

We report a case of plasmablastic lymphoma after the use of temozolomide in a patient with glioblastoma; this patient received the standard dose and schedule of this alkylating drug.

Case report. A 73-year-old right-handed man presented with a generalized seizure at age 71 years and was diagnosed with an enhancing cystic mass within the left frontal lobe. He had a subtotal resection of the mass and the pathology revealed a methylguanine methyltransferase (MGMT)–methylated glioblastoma. He was treated with standard radiation and temozolomide at 75 mg/m^2/day for 6 weeks followed by 6 cycles of adjuvant temozolomide at 200 mg/m^2 per day for 5 days each month.[1] He completed therapy without complications and was then observed with surveillance MRI scans every 2 months.

He remained stable but 2 months after stopping adjuvant temozolomide was noted to have an enhancing lesion within his left maxillary sinus on MRI (figure, A and B). After treatment with antibiotics failed to resolve the lesion, he underwent a partial resection of the lesion. The pathology was plasmablastic lymphoma with the following marker profile: CD20+, CD138+, MUM1+, EBER (Epstein-Barr virus [EBV] RNA)+, CD56−, HHV8−. The Ki-67 proliferation index was 70%.[3]

His initial staging included a bone marrow biopsy, which showed a mildly hypercellular marrow with trilineage hematopoiesis and no morphologic evidence of lymphoma. CSF analysis showed no evidence for a monoclonal B-cell or unusual T-cell population by cytology, flow cytometry, or immunoglobulin heavy chain (IgH) rearrangement. A fluorodeoxyglucose-PET (FDG-PET) scan of the body demonstrated intense uptake in the left maxillary sinus but no additional sites of FDG-avid disease. Chest, abdomen, and pelvis CT scans showed no evidence of any lymphomatous involvement outside the left maxillary sinus. HIV and hepatitis serologies were negative. His subsequent brain MRIs remained stable without evidence of recurrent glioblastoma.

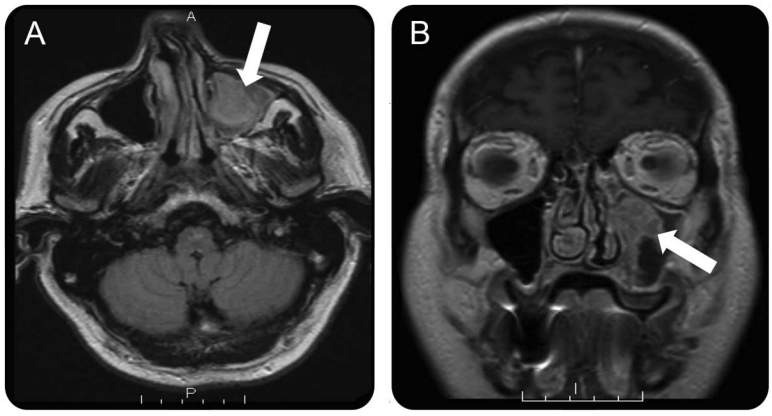
He was diagnosed with stage IAE plasmablastic lymphoma and was treated with 4 cycles of EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and intrathecal methotrexate followed by focal radiation to the maxillary sinus. He achieved a complete response to this treatment and remains alive without progression of his lymphoma or glioblastoma, 24 months after diagnosis of the former and 52 months after diagnosis of the latter.

Discussion. Temozolomide is a DNA-alkylating agent used to treat glioblastoma, recurrent malignant gliomas, and metastatic malignant melanoma.[1,4] It is considered to be first-line therapy in newly diagnosed glioblastoma and when used in the standard regimen (5 out of 28 days) confers a significant survival advantage compared to radiation alone.[1]

Because temozolomide is a DNA-damaging agent, there is concern for the induction of secondary malignancies. To our knowledge, there are 16 reported cases of secondary malignancies or hematopoietic disorders in brain tumor patients treated with temozolomide: 10 with myelodysplasia, 2 with aplastic anemia, and 4 with non-Hodgkin lymphoma.[2,5] Among the 4 patients with non-Hodgkin lymphoma, 1 case was a plasmablastic lymphoma in a 58-year-old patient treated with 25 cycles of dose-dense (nonstandard therapy) temozolomide[6]; the EBV status in these 4 cases is not published.

Plasmablastic lymphoma is a distinct but rare form of mature B-cell non-Hodgkin lymphoma. It is most commonly observed in patients with HIV infection and with CD4 counts less than 200/μL and has been associated with EBV infection.[7] In patients with plasmablastic lymphoma who are HIV-negative, the etiology is thought to be secondary to other forms of immunosuppression, including prolonged steroid use or post-transplantation. This patient did not use steroids during adjuvant temozolomide, nor was the patient on

Figure Enhancing mass in the left maxillary sinus after treatment with standard therapy for glioblastoma



(A) Postcontrast T1-weighted axial MRI and (B) postcontrast T1-weighted coronal MRI demonstrate an enhancing left maxillary mass (arrows).

phenytoin or carbamazepine therapy. Furthermore, the left maxillary sinus was not part of the portal dosimetry used during radiation therapy. Thus, it is hypothesized that the likely mechanism in this patient was impairment of cell-mediated immunity by temozolomide, allowing EBV reactivation and viral oncogenesis.

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