Regression of Recurrent High-Grade Glioma with Temozolomide, Dexamethasone, and Levetiracetam: Case Report and Review of the Literature

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INTRODUCTION
Recurrent glioma of the brain is an incurable disease. Treatment options for recurrent glioma include chemotherapy, radiotherapy, surgery, and palliation. Temozolomide appears to be effective in patients with recurrent high-grade gliomas.¹ In vitro and retrospective studies have shown dexamethasone and levetiracetam to inhibit tumor proliferation directly and to increase sensitivity to chemotherapy.²

CASE DESCRIPTION
A 35-year-old woman presented with headache, vomiting, executive memory loss, and decreased sleep. Computed tomography of the brain showed an ill-defined heterogeneous mass 5 × 5 cm involving both frontal lobes and genu of corpus callosum. Multiple discrete, small calcifications were seen in the lesion. Significant perilesional edema was seen in bilateral frontal white matter (Figure 1). Magnetic resonance imaging (MRI) of the brain showed a bifrontal lesion with a lobulated irregular rim-enhancing diffuse hyperintense lesion with a central necrotic areas,

Figure 1. Computed tomography showing large bifrontal lesion with multiple calcifications and edema.
**CASE REPORT**

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Diffuse hyperintense enlargement of anterior corpus callosum, and extensive bifrontal white matter vasogenic edema (Figures 2 and 3). The diagnosis after imaging was high-grade butterfly glioma.

Bifrontal decompressive craniectomy and decompression of tumor was performed under general anesthesia. Postoperative computed tomography showed decompression and extensive bifrontal edema (Figure 4). The patient was unconscious for 5 days and received mechanical ventilation. Mannitol and dexamethasone were given. She slowly recovered with antiedema measures. Power and movement were normal, but cognition and memory were impaired initially.

The histopathology report was grade 3 anaplastic oligodendroglioma. MRI with contrast was performed and showed no residual lesion. She underwent radiotherapy and received temozolomide. Phenytoin and levetiracetam were given to control intermittent seizures. She underwent cranioplasty after 4 months.

During the follow-up interval, the patient experienced progressive deterioration of memory. MRJ performed 5 years after surgery showed an intensely enhancing recurrence in the region of the right caudate nucleus measuring $4 \times 3 \text{ cm}$ (Figure 5). Magnetic resonance spectroscopy showed increased choline and decreased N-acetyl aspartate (Figure 6). Repeat surgery and radiation were suggested but refused. The patient was treated with temozolomide and dexamethasone. Temozolomide was given 250 mg/day for 5 days in 28-day cycles. Levetiracetam was continued. She was given multivitamins also.

MRI with contrast performed 10 months later showed $\geq 90\%$ decrease in the enhancing portion, suggestive of remission (Figure 7). The patient continues to receive intermittent temozolomide therapy and antiepileptic treatment with levetiracetam. The positive response could be due to the combined effects of temozolomide, dexamethasone, and levetiracetam. The rare possibility of spontaneous remission also should be considered.

**DISCUSSION AND REVIEW OF LITERATURE**

High-grade glioma is an aggressive form of brain cancer. Treatment usually entails biopsy or resection if safe, followed by radiotherapy. Despite aggressive treatment, high-grade malignant gliomas (anaplastic astrocytoma and glioblastoma multiforme) have a poor prognosis. Most malignant gliomas (at least 70%) recur after initial treatment. Responses in recurrent disease are not enduring, and quality of life because of tumor growth is poor. Tumors with oligodendrogial components have improved responses to therapy and a better prognosis than other malignant gliomas.

Prospective trials confirmed that 1p/19q codeletion represents a strong and independent favorable prognostic factor in anaplastic oligodendrogial tumors. Temozolomide, a novel, oral alkylating chemotherapeutic agent, has shown efficacy in treatment of high-grade glioma with a favorable safety profile. Temozolomide is an imidazotetrazine agent and is effective in recurrent glioma. The active metabolite is monomethyl triazeno imidazole carboxamide, and cytotoxicity is primarily due to methylation at the $O^6$ position of guanine. Temozolomide also acts as an inhibitor of DNA mismatch repair and can induce apoptosis.

Repeat surgery, reirradiation, and second-line monotherapy or combination therapy all are directed primarily at reducing tumor burden and extension. There are few studies reporting the results of reoperations during the treatment of the anaplastic astrocytoma, and the actual role of repeat surgery is controversial. Temozolomide, which began to be used in chemotherapy of
Glial tumors within the past 10 years, is being accepted as a promising agent in the treatment of patients with recurring high-grade glioma. It has been reported that temozolomide, higher doses of which are tolerated better compared with nitrosourea chemotherapy agents, has a more favorable safety profile. Moreover, in vitro studies have demonstrated the synergistic interaction between temozolomide and radiotherapy. Temozolomide chemotherapy showed a significant objective response rate of 35% in recurrent anaplastic astrocytoma.

Antiepileptic drugs may have an unrecognized impact in modulating O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein that has an important role in tumor cell resistance to alkylating agents. Levetiracetam is the most potent MGMT inhibitor among several antiepileptic drugs with diverse MGMT regulatory actions. In vitro, when used at concentrations within the human therapeutic range for seizure prophylaxis, levetiracetam decreases MGMT protein and messenger RNA expression levels. Levetiracetam may provide a survival benefit in patients with glioblastoma who receive temozolomide-based chemotherapy.

Dexamethasone reduces brain tumor—associated vascular permeability by reducing the response of the vasculature to tumor-derived permeability factors (vascular permeability factor, also known as vascular endothelial growth factor). Vascular endothelial growth factor expression by tumor cells also is reduced. Dexamethasone, via the glucocorticoid receptor pathway, is shown to directly inhibit vascular endothelial growth factor production in glioblastoma cells. There is also a growing body of evidence that dexamethasone inhibits glioma cell proliferation in vitro and tumor growth in vivo. Peddi et al. reported a case of a patient who had significant regression of glioblastoma multiforme with dexamethasone and levetiracetam alone.

Kyrkis et al. published a report on modulation of glioma risk and progression by dietary nutrients and anti-inflammatory agents. Vitamins A, C, D,
and E and their derivatives may have anticancer properties and may modulate gliomagenesis. Retinoids are chemical compounds related to vitamin A. They strongly inhibit the proliferation and migration of cells in primary cultures of human glioblastoma multiforme. In 1 study, ascorbyl stearate, a lipophilic derivative of ascorbic acid (or vitamin C), had antiproliferative and apoptotic effects on T98G glioma cells, probably through modulation of insulin-like growth factor receptor 1 expression and consequent facilitation of programmed cell death. Vitamin D receptor mRNA levels have been reported to be significantly higher in glioblastomas than in both low-grade and anaplastic astrocytomas, and there is in vitro evidence that vitamin D metabolites alone or in combination with retinoids may be potentially useful agents in the differentiation therapy of human malignant gliomas. Studies on the effects of several tocopherols (the most abundant and common of which is vitamin E) on the proliferation and death of murine glioma C6 cells demonstrated that gamma-tocopherol was an effective inhibitor of cell cycle progression.14

Spontaneous regression of cancer is reported in virtually all types of human cancer, although the greatest number of cases are reported in patients with neuroblastoma, renal cell carcinoma, malignant melanoma, and lymphomas/leukemias. Mechanisms proposed for spontaneous regression of human cancer include immune mediation, tumor inhibition by growth factors and/or cytokines, induction of differentiation, hormonal mediation, elimination of a carcinogen, tumor necrosis and/or angiogenesis inhibition, psychological factors, apoptosis, and epigenetic mechanisms.15 The processes involved in spontaneous regression of tumors are mainly related to the process of apoptosis and the activity of the immune system as well as to conditions in the tumor microenvironment. Therefore, such processes are occasionally linked more or less directly to the oncogenic suppressors of DNA. Among tumors that demonstrate spontaneous regression, neuroblastoma is the most studied with regard to the presence of alterations of the genome, with an oncogenic or oncosuppressor effect.16 Large, clinically

Figure 4. Postoperative computed tomography scan showing decompression of tumor and edema.

Figure 5. Magnetic resonance imaging showing intensely enhancing recurrence in the region of the right caudate nucleus.
symptomatic optic gliomas may undergo spontaneous regression.\textsuperscript{17} Loh et al.\textsuperscript{18} documented that patients with subtotal removal of cerebellar astrocytoma can have arrested tumor growth or spontaneous tumor regression during long-term follow-up.

CONCLUSIONS

This is a report of a middle-aged woman with corpus callosal anaplastic glioma who had recurrence after surgery and chemoradiotherapy. She experienced near total remission after the recurrence with temozolomide, levetiracetam, and dexamethasone. A few similar cases of regression of high-grade glioma with these drugs have been reported in the literature. Similar reports give more hope in the treatment of recurrent high-grade glioma.

REFERENCES


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