Improvement in Visual Fields After Treatment of Intracranial Meningioma With Bevacizumab

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Abstract: High-grade (World Health Organization [WHO] Grade II and III) meningiomas constitute a minority of all meningioma cases but are associated with significant morbidity and mortality, due to more aggressive tumor behavior and a tendency to recur despite standard therapy with resection and radiotherapy. They display a higher degree of vascularity than WHO Grade I meningiomas and produce angiogenic and growth factors, including vascular endothelial growth factor (VEGF). Bevacizumab, a humanized monoclonal antibody against VEGF-A, has been used in the treatment of recurrent or progressive meningiomas resistant to standard therapy. We report a patient with a recurrent left frontotemporal meningioma and associated-vision loss who experienced substantial visual field recovery after 3 cycles of bevacizumab. In addition, we provide a review of the literature regarding the efficacy of bevacizumab in the treatment of recurrent meningiomas.

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Meningiomas account for approximately one-third of all primary brain tumors and are the most common tumor of the central nervous system (1). Although the majority of meningiomas are classified as the World Health Organization (WHO) Grade I, 20%–30% of patients undergo progression to Grade II (atypical) and Grade III (anaplastic) tumors (1,2). Atypical and anaplastic meningiomas tend to behave more aggressively and progress despite standard management with gross total resection and radiotherapy. Effective treatment for these high-grade tumors is lacking (3). Bevacizumab is a monoclonal antibody against vascular endothelial growth factor-A (VEGF-A) (vascular permeability factor) and currently approved by the Federal Drug Administration as first-line treatment for metastatic renal cell and metastatic non–small cell lung carcinoma, second-line treatment for glioblastoma, and first- and second-line treatment for metastatic colorectal cancer (http://www.cancer.gov/cancertopics/druginfo/fda-bevacizumab). It has demonstrated efficacy in improving hearing and reducing tumor size in a subset of neurofibromatosis Type 2 (NF2) patients with vestibular schwannomas (4). In addition, it stabilized tumor size in meningioma patients in a few retrospective case series and case reports (5–9). We report a patient with a progressive intracranial meningioma who experienced transient but significant improvement in visual fields while treated with bevacizumab.

CASE REPORT

A 57-year-old man presented with 3 weeks of progressive personality changes, slowness, and memory difficulties noted by his pastor in church. Medical history was significant for a benign right-sided orbital-maxillary tumor of unclear histopathology at the age of 12 years. He was treated with surgical resection, radiation therapy with 52 Gy, and enucleation of the right eye. Initial neurologic examination in our clinic was only notable for impaired orientation, attention, and recall. Magnetic resonance imaging (MRI) of brain revealed a 6.7 × 6.1 × 7.6-cm extra-axial mass in the left frontotemporal lobe, which encroached upon but did not enter the optic canal (Fig. 1A). The appearance of the lesion was highly suggestive of

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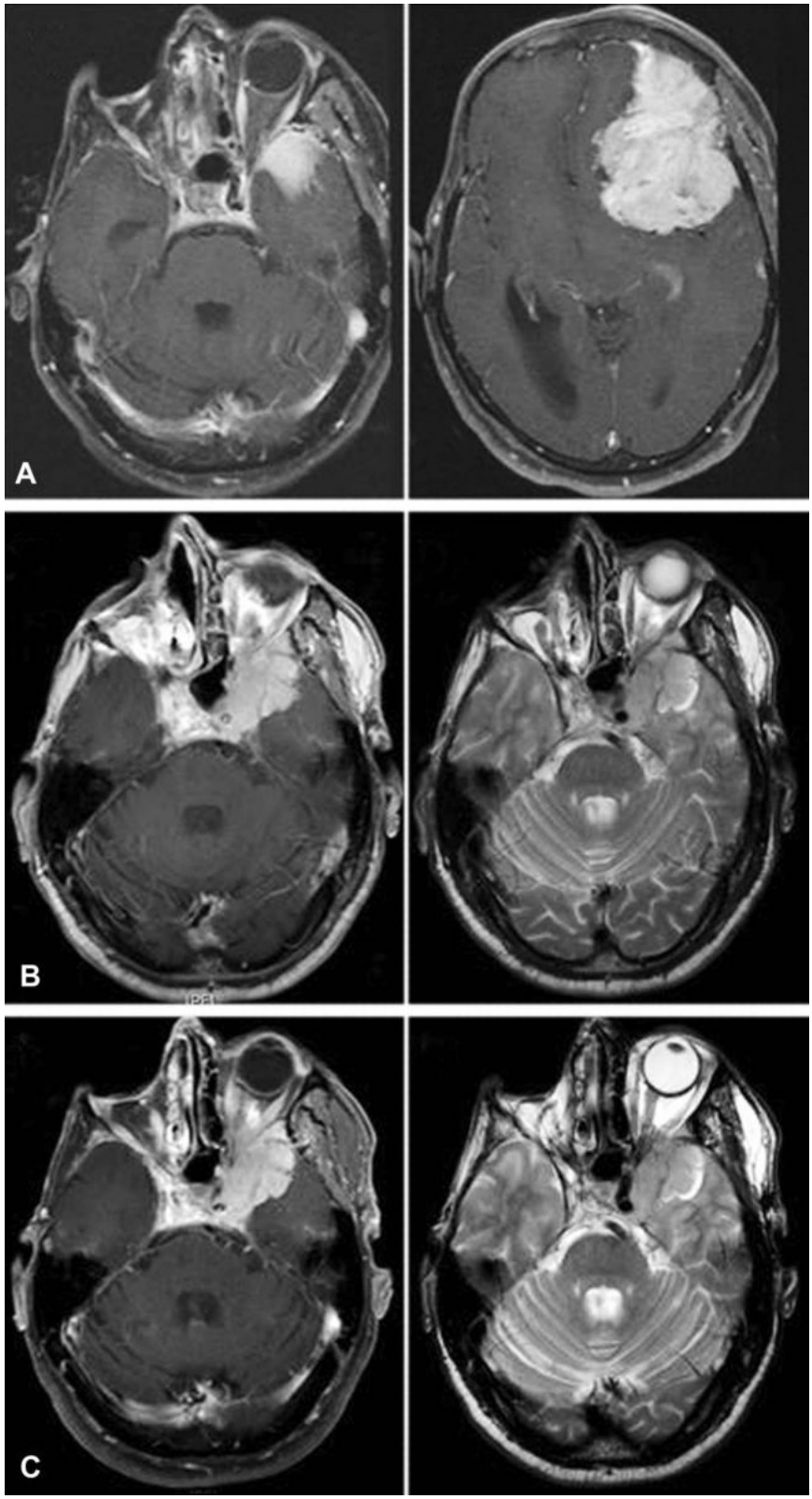

FIG. 1. Left frontotemporal meningioma. **A**. At presentation, postcontrast T1 axial MRI shows tumor in the left temporal lobe extending superiorly into the left frontal lobe but not entering the left optic canal. **B**. Approximately, 8 years after initial presentation, postcontrast T1 axial (left) and T2 axial (right) scans reveal enlargement of the tumor with extension into the left orbital apex and cavernous sinus. **C**. After 3 cycles of bevacizumab, there is no change in the extent of tumor or peritumoral edema on postcontrast T1 axial (left) or T2 axial (right) images. MRI, magnetic resonance imaging.

meningioma, likely radiation-induced, given the patient's treatment history. Visual activity was 20/20 in the left eye with mild optic disc pallor and intact visual field by confrontation. Automated field testing was precluded by the patient's confusion. He underwent gross total resection of the mass by left frontotemporal craniotomy, and pathology was consistent with a WHO Grade 1 meningioma. His cognition recovered fully after surgery, and he was monitored with yearly MRIs.

Three years later, brain MRI showed tumor recurrence in the left frontal lobe at its posterior and medial margins and along the left greater sphenoid wing, including the left lateral cavernous sinus, clival wall, Sylvian fissure, and posterior left orbit. Visual function was normal in the left eye (visual acuity of 20/20), including automated field testing (Fig. 2A). Two months later, he underwent partial tumor resection, and pathology was consistent with a recurrent WHO Grade 1 meningioma. Further management with radiation was deferred because of the proximity of the tumor to the left optic nerve.

Approximately 4½ years after initial presentation, MRI showed mild tumor growth in the left cavernous sinus and orbital apex. An inferior arcuate defect was detected on automated visual field testing. Despite involved-field radiotherapy (5,200 cGy in 26 fractions), the patient progressed clinically and radiographically. Seven months later, the left visual field showed mild superior and inferior arcuate defects yet acuity remained 20/20. He was enrolled in a Phase 2 clinical trial with PTK787 (vatalanib), an oral tyrosine kinase inhibitor against VEGF-R2 and platelet-derived growth factor receptor (PDGFR), but only received a few cycles of treatment due to hepatotoxicity. He stabilized clinically and radiographically and was monitored with MRIs every 3 months.

Seven years and 9 months after initial presentation, progressive tumor growth in the left superior frontal lobe prompted treatment with gamma knife radiosurgery (14 Gy) to 2 frontal nodules. Four months later, the patient reported decreased vision in the left eye. Acuity was 20/30, and there was increasing optic disc pallor and progressive visual field loss (Fig. 2B). There was tumor progression in the left middle fossa on MRI (Fig. 1B), and the patient was enrolled in a Phase 2 clinical trial using bevacizumab for recurrent or progressive meningioma, administered at 10 mg/kg intravenously every 2 weeks. One month later, after 3 cycles of bevacizumab, there was improvement in the left visual field (Fig. 2C). MRI revealed slight decrease in tumor size but no change in peritumoral edema (Fig. 1C) or apparent diffusion coefficient sequences. The patient tolerated bevacizumab well except for transient hypertension, fatigue, and anorexia.

Eight years and 5 months after presentation, visual acuity declined to 20/50 with worsening of the left visual field despite continuing bevacizumab. MRI showed reduction in size of the left frontal mass but enhancing lesions in

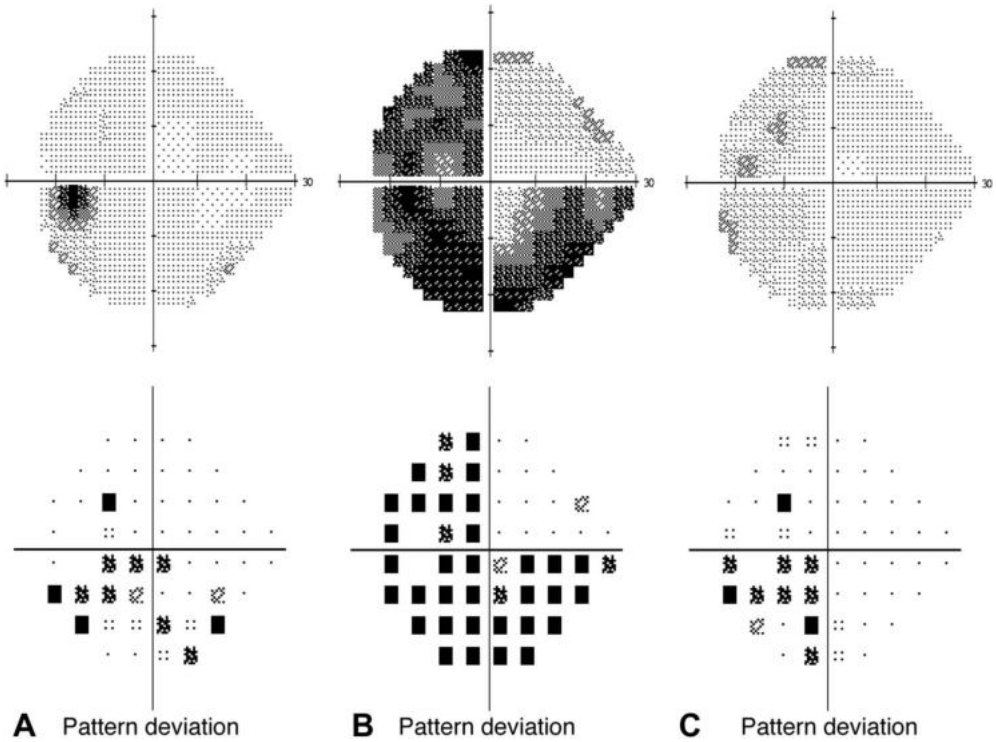

FIG. 2. Automated visual fields. **A**. Three years after initial presentation, the left visual field is normal. **B**. Seven years and 9 months after presentation, there is superior and inferior visual field loss. **C**. After 3 cycles of bevacizumab, there is improvement in the left visual field.

the middle cranial fossa remained unchanged. Given the refractory nature of the tumor, bevacizumab was discontinued after 11 cycles. The patient was started on Sandostatin LAR (30 mg intramuscularly) but also wished to resume bevacizumab given his previous favorable response. He has been on combined Sandostatin LAR (40 mg intramuscularly every month) and bevacizumab (10 mg/kg intravenously every 2 weeks). Visual function has continued to worsen to a small island of residual vision in the left nasal hemifield with acuity of 20/400. Ten years after initial presentation, MRI showed progressive disease. A summary of his clinical treatment course is shown in **Supplemental Digital Content** (Figure 1, http://links.lww.com/WNO/A158).

DISCUSSION

Most meningiomas are benign (WHO Grade I), do not produce significant neurologic deficits, and can be managed successfully with resection and/or radiation therapy. WHO Grade II (atypical) and Grade III (anaplastic) meningiomas display much more aggressive and invasive behavior and can cause considerable morbidity and mortality. These tumors are frequently not completely resectable, and medical therapy remains the last option. However, the use of chemotherapeutics (temozolomide, hydroxyurea, irinotecan, cyclophosphamide + doxorubicin + vincristine), hormonal therapies, and interferon alfa-2b are limited by their lack of efficacy (3). On a molecular level, meningiomas are highly vascular and characterized by overexpression of growth factors and their receptors, including VEGF, PDGF, insulin-like growth factor, and transforming growth factor beta. Thus, therapies targeted at these molecular substrates have assumed an increasingly important role in the management of high-grade meningiomas.

VEGF promotes proliferation and survival of endothelial cells, increases expression of adhesion molecules, and enhances vascular permeability (10), increasing tumor vascularity and facilitating nutrient delivery to the tumor. Levels of VEGF and VEGF receptors increase with meningioma grade and correlate with extent of peritumoral brain edema (3). In addition, elevated VEGF levels are seen in radiation necrosis, likely driven by a combination of radiation-induced endothelial cell dysfunction, tissue hypoxia, and necrosis, leading to increased vascular permeability and edema (11,12). Patients with more aggressive meningiomas are at increased risk of peritumoral edema from both the tumor itself and radiation-related changes.

Bevacizumab is a monoclonal antibody against VEGF-A and one of its main effects is the normalization of tumor vasculature, resulting in improved oxygen and drug delivery to tumor cells and reduction of tissue hypoxia (10). Tissue hypoxia promotes resistance of tumor cells to radiation and certain cytotoxic drugs and creates a microenvironment that favors survival of malignant over normal cells (10). Bevacizumab can potentially reverse this imbalance and restore a normal cellular milieu. In addition, bevacizumab is known to decrease radiation necrosis (11–13). In a randomized placebo-controlled trial, only patients who received bevacizumab (but none who received placebo) had neurologic improvement and met MRI response criteria on postcontrast T1 and T2/FLAIR imaging (11). Tye et al (13) recently reviewed 71 published cases of radiation necrosis treated with bevacizumab and found that bevacizumab led to radiographic improvement in 97% of patients, including a median decrease of 63% in enhancement on postcontrast T1 imaging and 59% decrease in T2/FLAIR hyperintensity. Furthermore, 79% of cases had improvement in Karnofsky performance status (13).

Our report is unique in demonstrating a measurable functional outcome in a patient with radiation-induced intracranial meningioma, documented in several visual-field examinations. Our findings are comparable with hearing improvement observed in NF2 patients treated with bevacizumab for progressive vestibular schwannomas (4). Bevacizumab given at 5 mg/kg every 2 weeks led to improved word-recognition scores on hearing response testing in 4 of 7 NF2 patients, and the response was sustained over 11–16 months. Radiographically, bevacizumab decreased schwannoma size by a median of 26% in 9 of 10 NF2 patients, and in 1 patient, tumor blood flow and volume decreased by 77% and 51%, respectively. No significant change in contrast enhancement was seen on MRI.

Single-agent bevacizumab has demonstrated some efficacy in intracranial meningiomas in a small number of retrospective case series and case reports (5–9), although the duration of response was less robust than in schwannoma patients. In one case series of 15 patients, the best radiographic response achieved was stable disease (SD) by response assessment in neuro-oncology criteria in 13 patients (7). Two patients had decreased enhancement on MRI but did not meet partial response criteria. A decrease in T2/FLAIR hyperintensity was seen in only 6 patients, likely because most T2/FLAIR changes were related to radiation necrosis rather than peritumoral edema. In another case series, 11 of 14 patients achieved SD (5). This study included patients receiving bevacizumab as single agent (4 of 14) and with other chemotherapeutics (10 of 14) as well as meningiomas of all histologic grades. The third case series evaluated efficacy of bevacizumab in 15 NF2 patients with 48 meningiomas. Radiographic response by volumetric analysis was seen in 29% (14 of 48) of meningiomas and 7% (1 of 15) of patients. Median duration of treatment response was 3.7 months. Overall, median progression-free survival (PFS) in these case series ranged from 6.5 months (7) to 15–18 months (5,6). Median overall survival was reported in 1 case series only (15 months) (7). Our case report mirrors some of the above results, in that best radiographic response achieved was SD and duration of response was short lived (5 months). Therefore, our patient's clinical

improvement was more likely related to bevacizumab-induced reduction in postradiation injury and peritumoral edema, rather than a direct effect on meningioma size.

Studies investigating the use of other growth factor inhibitors have shown modest results. In a Phase II study of imatinib, a PDGFR inhibitor, patients with atypical/anaplastic meningiomas had a median PFS of 2 months and PFS6 of 0% (14). Best radiographic response was SD in 9 of 19 patients (14). In another study, imatinib combined with hydroxyurea led to PFS6 of 46% (15). A Phase II trial of sunitinib, a tyrosine kinase inhibitor targeting VEGFR, PDGFR, and KIT, demonstrated median PFS of 5.2 months in those with WHO Grade II/III meningiomas and a PFS6 of 42% (16).

It is conceivable that targeting one signaling pathway is insufficient to produce a durable treatment response. Further insights into the molecular biology of meningiomas are needed to clarify the relative significance of VEGF in meningioma pathogenesis. In addition, since it is unclear if and how much direct cytotoxic effect antiangiogenic agents have, one important question to address is whether coadministration with a cytotoxic drug will enhance treatment efficacy. Finally, prospective trials will help to shed light on long-term efficacy of bevacizumab as monotherapy (clinical trial number NCT01125046) and in combination with other agents (NCT00972335; bevacizumab and everolimus).

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