

Bevacizumab for the treatment of post-stereotactic radiosurgery adverse radiation effect

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Abstract

Background: Adverse radiation effect (ARE) is one of the complications of stereotactic radiosurgery. Its treatment with conventional medications, such as corticosteroids, vitamin E, and pentoxifylline carries a high risk of failure, with up to 20% of lesions refractory to such medications. In addition, deep lesions and those occurring in patients with significant medical comorbidities may not be suitable for surgical resection. Bevacizumab is an antiangiogenic monoclonal antibody against vascular endothelial growth factor, a known mediator of cerebral edema. It can be used to successfully treat ARE.

Case Description: An 85-year-old man with a history of small-cell lung cancer presented with metastatic disease to the brain. He underwent stereotactic radiosurgery to a brain metastasis involving the right external capsule. Three months later, the lesion had increased in size, with significant surrounding edema. The patient developed an adverse reaction to steroid treatment and had a poor response to treatment with pentoxifylline and vitamin E. He was deemed a poor surgical candidate because of his medical comorbidities. He was eventually treated with 3 doses of bevacizumab, and the treatment resulted in significant clinical improvement. Magnetic resonance imaging showed some decrease in the size of the lesion and significant decrease in the surrounding edema.

Conclusions: Bevacizumab can be successfully used to treat ARE induced by stereotactic radiosurgery in patients with cerebral metastases. It is of particular benefit in patients considered unsuitable for surgical decompression. It is also beneficial in patients with poor tolerance to corticosteroids and in patients who do not respond to other medications.

Key Words: Adverse radiation effect, bevacizumab, cerebral metastases, complication, stereotactic radiosurgery

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INTRODUCTION

Adverse radiation effect (ARE) is one of the complications of stereotactic radiosurgery.^[7] The pathophysiology of ARE involves damage to vascular endothelial cells, with subsequent vessel occlusion and coagulation necrosis.^[8] Symptoms are caused by surrounding vasogenic edema and subsequent mass effect.

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Medical management of ARE includes corticosteroids, vitamin E, and pentoxifylline.^[2,8] However, these treatments were not significantly effective in randomized controlled trials, with up to 20% of lesions refractory to medical treatment.^[2,8] Surgical decompression has been used for symptomatic lesions refractory to medical management.^[11] Recent reports suggest that deep lesions that are not readily accessible by a surgical corridor may be treated with laser-interstitial thermal therapy.^[3,5,9] However, those lesions occurring in patients with significant medical comorbidities may not be suitable for surgical intervention.

Bevacizumab is an antiangiogenic monoclonal antibody against vascular endothelial growth factor, a known mediator of cerebral edema. Bevacizumab was shown to be effective in the treatment of radiation-induced necrosis in patients with brain tumors.^[8]

CASE REPORT

An 85-year old man with a history of small-cell lung cancer presented with metastatic disease to the brain. The patient underwent stereotactic radiosurgery (Gamma Knife Perfexion, Elekta Inc., Stockholm, Sweden) to a 7.0 × 8.0 × 8.0 mm brain metastasis involving the right external capsule [Figure 1 left]. The tumor was prescribed a 20 Gy dose to the 45% isodose line with a gradient index of 2.91 [Figure 2].

Three months later, the patient developed new-onset imbalance. Magnetic resonance imaging (MRI) showed that the lesion had increased to 23.0 × 28.0 × 25.0 mm, with significant surrounding edema [Figure 1 middle]. The patient was initially treated with dexamethasone but developed significant proximal muscle weakness. He was then started on pentoxifylline and vitamin E but continued to experience significant deterioration in his activities of daily living. The patient was deemed a poor surgical candidate because of advanced congestive heart failure with low ejection fraction, superior vena cava syndrome, and carotid stenosis. However, his systemic disease remained under good control. He was treated with 3 doses of bevacizumab (7.5 mg/kg every 3 weeks for

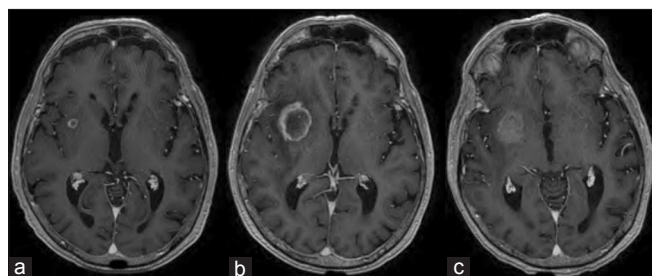


Figure 1: T1 magnetic resonance imaging of the brain, axial post-contrast sequences, showing right external capsule lesion before stereotactic radiosurgery (left), 3 months following stereotactic radiosurgery (middle), and after treatment with bevacizumab (right)

12 weeks). Of note, the bevacizumab doses were covered by the patient's health maintenance organization. Treatment resulted in significant improvement in activities of daily living, and the patient became functionally independent following the completion of the 3 treatment doses. MRI showed some decrease in the size of the lesion and a significant decrease in the surrounding edema [Figure 1 right].

DISCUSSION

This case describes a significant size increase in a brain metastasis following stereotactic radiosurgery. There is no noninvasive diagnostic study to differentiate tumor recurrence from ARE in post-stereotactic radiosurgery brain metastases.^[6] The lesion's rapid increase in size over a 3-month period suggested a diagnosis of ARE. Compared with the patient's original brain MRI study (before stereotactic radiosurgery), the study obtained on the day of stereotactic radiosurgery suggested a tumor growth rate that alone could not account for such rapid lesion growth. An ARE peak 3 months post-stereotactic radiosurgery has previously been described.^[4]

Symptomatic post-stereotactic radiosurgery brain metastases should be treated.^[6] For patients who are not surgical candidates, bevacizumab is an option. Although typically well-tolerated, side effects can include poor wound healing, intestinal perforation, and cerebrovascular accident.^[10] Recent bevacizumab use is an absolute contraindication to many surgical procedures.^[11] In addition, there is a significant cost to this medication, and it may not always be covered by a health maintenance organization. In patients with symptomatic ARE who are not surgical candidates, bevacizumab does provide a nonsurgical treatment option. The use of prolonged corticosteroid therapy for ARE should be avoided due

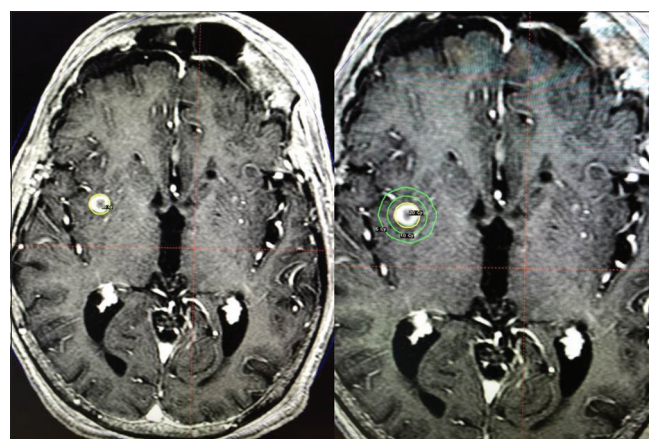


Figure 2: Planning magnetic resonance images for stereotactic radiosurgery to a lung-primary brain metastasis. The panel on the left depicts the tumor prescribed a 20 Gy dose to the 45% isodose line with a gradient index of 2.91. The right panel additionally shows the 10 Gy and 5 Gy lines

to significant steroid-related toxicities. Such nonsurgical patients who are symptomatic after stereotactic radiosurgery for brain metastasis should be evaluated for bevacizumab therapy.

CONCLUSION

Bevacizumab can successfully be used to treat ARE induced by stereotactic radiosurgery in patients with cerebral metastases. It is of particular benefit in patients unsuitable for surgical decompression. Rather than a prolonged course of corticosteroids, patients with post-stereotactic radiosurgery ARE should be evaluated for bevacizumab therapy.

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Authors' contributions

Conception and design: both authors; Acquisition of data: both authors; Analysis and interpretation of data: both authors; Drafting of the manuscript: Fanous; Critical revision of the manuscript for important intellectual content: both authors; Final approval of the manuscript: both authors.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Clark AJ, Butowski NA, Chang SM, Prados MD, Clarke J, Polley MY, *et al.* Impact of bevacizumab chemotherapy on craniotomy wound healing. *J Neurosurg* 2011;114:1609-16.
2. Dashti SR, Spalding A, Kadner RJ, Yao T, Kumar A, Sun DA, *et al.* Targeted intraarterial anti-VEGF therapy for medically refractory radiation necrosis in the brain. *J Neurosurg Pediatr* 2015;15:20-5.
3. Fabiano AJ, Alberico RA. Laser-interstitial thermal therapy for refractory cerebral edema from post-radiosurgery metastasis. *World Neurosurg* 2014;81:652 e1-4.
4. Fabiano AJ, McBride P, Prasad D, Plunkett RJ, Fenstermaker RA, Qiu J. Post-stereotactic radiosurgery radiation necrosis: The three-month peak. Presented at the American Association of Neurological Surgeons 83rd Annual Meeting, Washington DC, May 2-6, 2015.
5. Fabiano AJ, Qiu J. Delayed failure of laser-induced interstitial thermotherapy for postradiosurgery brain metastases. *World Neurosurg* 2014;82:e559-63.
6. Fabiano AJ, Qiu J. Post-stereotactic radiosurgery brain metastases: A review. *J Neurosurg Sci* 2015;59:157-67.
7. Kano H, Kondziolka D, Lobato-Polo J, Zorro O, Flickinger JC, Lunsford LD. T1/T2 matching to differentiate tumor growth from radiation effects after stereotactic radiosurgery. *Neurosurgery* 2010;66:486-91.
8. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, *et al.* Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys* 2011;79:1487-95.
9. Rao MS, Hargreaves EL, Khan AJ, Haffty BG, Danish SF. Magnetic resonance-guided laser ablation improves local control for postradiosurgery recurrence and/or radiation necrosis. *Neurosurgery* 2014;74:658-67.
10. Taugourdeau-Raymond S, Rouby F, Default A, Jean-Pastor MJ, French Network of Pharmacovigilance C. Bevacizumab-induced serious side-effects: A review of the French pharmacovigilance database. *Eur J Clin Pharmacol* 2012;68:1103-7.
11. Torcuator R, Zuniga R, Mohan YS, Rock J, Doyle T, Anderson J, *et al.* Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. *J Neurooncol* 2009;94:63-8.