

Role of *Boswellia Serrata* in Management of CNS Radiation Necrosis After Radiosurgery for Brain Metastases

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Abstract

Radiation necrosis (RN) is a concerning late toxicity after radiation therapy for brain metastases. The management of RN primarily depends on the extent of edema on imaging and presence of symptoms. Oral corticosteroids are the mainstay of management; however, they are not optimal for long-term management because of multiple side effects and drug interactions. *Boswellia serrata* is an extract derived from Indian frankincense, which is available as an over-the-counter supplement, and has been traditionally used in the treatment of asthma, arthritis and colitis due to its anti-inflammatory properties. Recent data have reported the benefits of *Boswellia* on reducing cerebral edema. We discuss a case report involving a patient with brain metastases treated with stereotactic radiosurgery who developed early RN and had a good response with resolution of postradiation edema with the use of *Boswellia*.

Keywords: Radiation necrosis, *Boswellia*, steroid, brain metastases, stereotactic radiosurgery

Case Summary

A 59-year-old woman with no significant past medical history presented with abdominal discomfort and elevated liver function tests. She was incidentally found to have a left upper quadrant abdominal mass. She underwent left robotic nephrectomy with pathology suggestive of multifocal clear-cell renal cell carcinoma, with a 9-cm and a 3.5-cm tumor, negative margins and 0/6 lymph nodes involved

(pT3 pN0). Systemic staging scans revealed right-sided, pleural-based enhancing nodules and pleural effusion. She had an F-18 fluorodeoxyglucose (FDG) PET/CT scan, which demonstrated hypermetabolic activity in the right pleural surface in the mid to lower hemithorax (SUV max 3.0), with no other distant metastases. She underwent video-assisted thoracoscopic surgery (VATS) biopsy of parietal pleural nodules, which confirmed metastatic renal cell carcinoma.

Baseline contrast-enhanced MRI of brain was negative for intracranial metastases. She was started on first-line systemic therapy with pembrolizumab and axitinib. Restaging scans revealed good response with improvement in small pulmonary nodules with minimal residual pleural thickening in the right lung base.

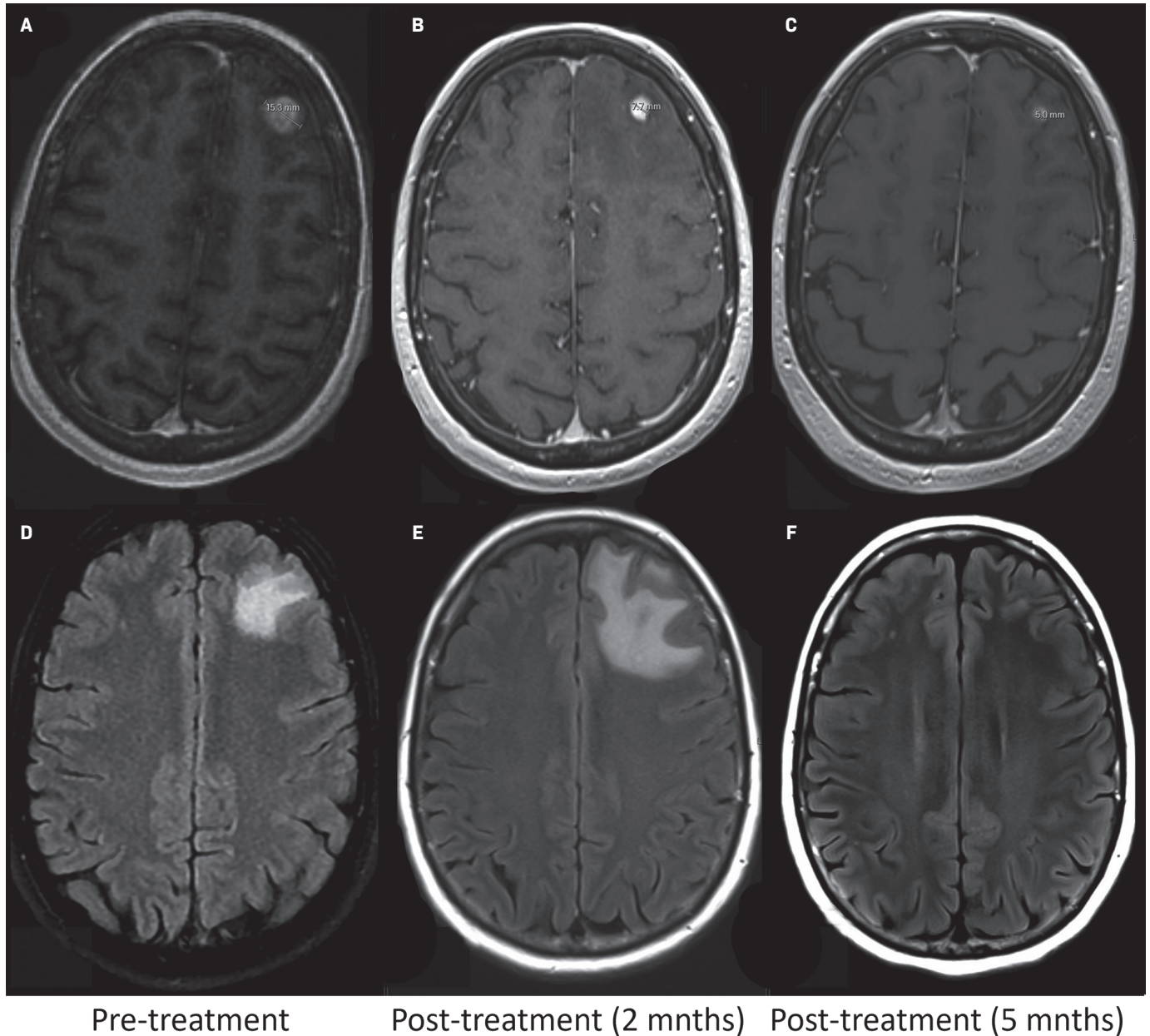
About 6 months after initial diagnosis, the patient presented with headaches and left-sided neck pain. A brain MRI with and without contrast revealed interval development of a 1.5 × 1.4-cm enhancing nodule in the left frontal lobe with mild to moderate surrounding vasogenic edema and mass effect. She also had an MRI of the cervical spine, which demonstrated multilevel degenerative changes but no metastatic disease. She was started on a short course of tapering

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Figure 1. Serial MRI imaging, with T1 postcontrast axial images (A-C) and T2 FLAIR images (D-F) demonstrate good tumor response (B, C), while there was increase in surrounding edema 2 months after fractionated stereotactic radiosurgery (E), which subsided after initiating Boswellia (F).



dexamethasone. She had no significant findings on her neurological examination and had an excellent performance status with a Karnofsky performance score of 90. Her baseline cognitive objective Patient-Reported Outcome Measurement Information System (PROMIS) score was 39/40. She completed fractionated stereotactic radiosurgery (fsRS) to her left frontal lesion to a dose of 24 Gy in 3 fractions using 4 volumetric-modulated arc

therapy (VMAT) arcs of 6 MV flattening filter-free photons. A planning target volume (PTV) was created using a 2-mm margin around the gross tumor volume (GTV). The conformity index was 0.95 and the GTV received a mean dose of 27 Gy. She tolerated the treatment well with no acute side effects and continued pembrolizumab every 3 weeks and axitinib 5 mg twice a day.

She continued to have occasional headaches immediately after treatment

and completed 2 short-term tapering doses of dexamethasone after her radiation treatment, with resolution of her headaches. Her follow-up brain MRI 2 months after treatment revealed a decrease in the left frontal enhancing lesion, but increased surrounding edema, consistent with grade 1 radiation injury, according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. She was instructed to begin over-the-counter Boswellia

MODALITY	MECHANISM OF ACTION	ADEQUATE FOR	SIDE EFFECTS / DISADVANTAGES
Oral corticosteroids	Anti-inflammatory by suppressing migration of leukocytes, Repress NF-KB regulated inflammatory genes	Grade 2-3, symptomatic patients	Myopathy, iatrogenic Cushing's syndrome, gastric ulcers, fluid retention, neuropsychiatric effects
Bevacizumab	VEGF inhibition	Steroid-refractory patients	Hemorrhage, thrombosis and impaired wound healing
Laser interstitial thermal therapy (LITT)	Ablates both tumor tissue and VEGF-producing reactive glial cells	Steroid-refractory patients	Operative morbidity, transient and permanent weakness, hemorrhage, seizures, and hyponatremia
Hyperbaric oxygen therapy	Increased central oxygen levels promote perfusion and healing	Steroid-refractory patients	Expensive, requires specialized facilities and significant time commitment
Oral pentoxifylline and vitamin E	Improved perfusion	Grade 1-2, asymptomatic patients	Poor response rates
<i>Boswellia serrata</i>	Herbal over-the-counter supplement with anti-inflammatory properties	Grade 1-3, asymptomatic and mildly symptomatic patients	Minimal, occasional gastrointestinal intolerance
Surgical resection	Removes necrotic tissue	Symptomatic patients with mass effect on imaging, unclear local failure vs necrosis	Operative morbidity

serrata 4.2 to 4.5 gms daily in divided doses. She was taking *Boswellia* 3 × 1200 mg capsules (TNV vitamin brand) and 2 × 450 mg capsules (GNC brand) daily equaling a total dose of 4.5 gms daily in 3 divided doses. She tolerated the drug well with mild fatigue. She did not have any nausea, vomiting, gastrointestinal intolerance or any other side effects. She had a follow-up brain MRI at 5 months and 8 months post-treatment, which was consistent with interval improvement of FLAIR enhancement and edema around the prior treated left frontal lesion. No other new enhancing lesions were noted. Her serial PROMIS scores were 40, 40 and 39 at 2, 5 and 8 months of follow-up, respectively. At the last follow-up, 8.5 months after fSRS, she had remained free of headaches or any new neurological symptoms or signs.

Imaging Findings

A baseline, pretreatment brain MRI revealed a 14 × 15-mm post-contrast enhancing lesion in the left frontal lobe (**Figure 1A**) with minimal

surrounding edema (**Figure 1D**). Post-treatment scans 2 months after completing fSRS revealed a decrease in the left frontal lobe enhancing lesion, measuring 8 × 7 mm (**Figure 1B**). There was extensive increase in surrounding T2 FLAIR signal abnormality compatible with edema, measuring 5.6 × 3.6 cm in perpendicular diameters (**Figure 1E**). Further follow-up brain MRI at 5 months after treatment showed continued decrease of the enhancing lesion in the left frontal lobe (**Figure 1C**). There was significant decrease in surrounding T2 FLAIR edema, which was now 1.4 × 0.8 cm (**Figure 1F**). This corresponded to a > 90% response per updated Response Assessment in Neuro-Oncology (RANO) criteria with measurement of sum of product of perpendicular diameters (SPPDs).¹ The irregular enhancing lesion within the left frontal lobe and surrounding edema continued to decrease, as shown in a brain MRI at an 8-month follow-up. No increase in perfusion around the treated metastases was noted on follow-up imaging at 5 and 8 months, and there was no evidence of new enhancing lesions in the brain parenchyma.

Diagnosis

CTCAE v5.0 Grade 1 radiation injury after fSRS for brain metastases

Discussion

Radiation necrosis (RN) is a dose-limiting late toxicity after radiation therapy for brain metastases. With advancements in radiation techniques and systemic therapies, patients with brain metastases tend to live longer, making late toxicities such as RN more relevant. Within the context of brain metastases, the true incidence of RN is hard to estimate and probably lies between 5% and 20%.^{2,3} Using primarily imaging-based diagnosis, Minniti et al reported a 24% incidence of RN (14% symptomatic, 10% asymptomatic).⁴ Although the pathophysiology of RN is multifactorial, vascular injury and glial cell damage are attributed. Management of RN primarily depends on symptoms and the extent of edema on imaging. **Table 1** summarizes various treatment options for managing cerebral radiation necrosis. Oral corticosteroids (such as dexamethasone) are the preferred first line of management

for symptomatic patients. However, corticosteroids often fail to control RN and are not optimal for long-term management because of multiple side effects and drug interactions. Many patients may require steroids for a long duration and are at risk for chronic steroid toxicity such as myopathy, iatrogenic Cushing's syndrome, gastric ulcers, etc.

Multiple other treatment modalities have been tried with limited success. Bevacizumab (humanized monoclonal antibody against VEGF) is used to treat steroid-refractory RN. A pooled analysis involving 71 patients showed that bevacizumab had a radiographic response rate of 97% and clinical improvement rate of 79% with a mean decrease in dexamethasone dose of 6 mg.⁵ As such, bevacizumab appears to be a promising agent; however, the durability of response and toxicities associated with bevacizumab, such as hemorrhage, thrombosis and impaired wound healing, must be considered.^{3,6} Multiple other treatment modalities have been tried with limited success, including hyperbaric oxygen therapy, oral pentoxifylline and vitamin E, and laser interstitial thermal therapy (LITT), and their use is not well established.⁷ Surgical resection when feasible can provide control, relieve the mass effect, and provide pathological confirmation, but is associated with postoperative complications. In this context, evaluation of newer agents effective in preventing and managing cerebral edema after radiation therapy is warranted.

Easily available as an over-the-counter supplement, *Boswellia serrata* is an extract derived from Indian frankincense. It has been traditionally used in treatment of asthma, arthritis and colitis, given its anti-inflammatory properties. Recent data have reported the beneficial effects of *Boswellia* on

reducing cerebral edema.⁸ Kirste et al conducted the first randomized clinical trial to study the efficacy of *Boswellia* in reducing cerebral edema in brain tumor patients treated with radiation, and observed that 60% of patients receiving *Boswellia* reached a > 75% decrease in edema compared to only 26% in the placebo group.⁸ The *Boswellia* preparation has reported no adverse effects. No studies have reported differential response rates based on *Boswellia* dose and preparation used so far. In another study, a *Boswellia* acid abstract given to 20 glioblastoma patients after surgery and chemoradiation led to considerable decrease in cerebral edema with maintained quality of life.⁹

In our patient, we were able to achieve a significant response with *Boswellia* with near complete resolution of edema, and our patient was able to avoid long-term steroid use. In this context, *Boswellia* can be used in various settings including decreasing existing cerebral edema, prophylactic risk reduction of symptomatic necrosis, and in management of RN, especially since it has no adverse effects. Drug interactions with steroid use become a particular concern in the modern era given the emergence of immunotherapy for several cancers. *Boswellia* can potentially decrease steroid dependence in these patients, thus reducing the risk of several side effects. Further prospective studies to evaluate the response rate with the use of *Boswellia* in patients who develop significant edema after fSRS for brain metastases is warranted.

Conclusion

Radiation necrosis is a dose-limiting late toxicity after stereotactic radiosurgery for brain metastases. *Boswellia serrata* is a promising treatment option for early radiation injury

with no added side effects seen in our patient. It may be a suitable alternative to long-term steroid use. Further prospective studies evaluating the response rates with *Boswellia* for radiation necrosis are warranted.

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