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Radiation necrosis: Now you see it, now you don't

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CASE SUMMARY

A 61-year-old woman with a large-cell neuroendocrine carcinoma of the lung, at her 10-month post-lobectomy and chemotherapy status had developed a 1.3 × 1.8 × 1.4-cm left thalamic/tectal lesion (Figure 1). Consideration was noted for metastasis, and it was treated with Gamma Knife stereotactic radiosurgery (SRS, Figure 2).

The lesion initially regressed (Figure 3). However, at 14 months post-SRS, the patient developed fatigue, right-sided hemianesthesia, thermoanesthesia and diplopia, and enhancement at the SRS site (Figure 4), which persisted despite dexamethasone treatment (Figures 5 and 6). After 4 doses of bevacizumab, the patient's symptoms stabilized, but she experienced a generalized tonic-clonic seizure, at which time magnetic resonance imaging (MRI) demonstrated near-resolution of enhancement (Figure 7). The lesion returned to its size at onset of radiation necrosis (RN) symptoms, and remained stable through 37 months post-SRS (Figure 8).

The patient was without evidence of active disease 45 months after SRS, with stable hemianesthesia, hemithermoanesthesia, exotropia, hypertropia, and diplopia.

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IMAGING FINDINGS

At diagnosis of presumed brain metastasis, axial T1 contrast-enhanced MRI demonstrated a 1.3 × 1.8 × 1.4-cm cystic, peripherally enhancing mass in the left thalamus/tectum causing obstructive hydrocephalus (Figure 1). At 11 months post-SRS, axial T1 contrast-enhanced MRI showed no discrete mass, mass-effect, midline shift or abnormal lesion (Figure 3). Three months later, axial T1 contrast-enhanced MRI demonstrated enhancement at the site of treatment (Figure 4). At 18 months post-SRS, axial T1 contrast-enhanced MRI showed radiographic stability (Figure 5). Advanced imaging techniques for differentiation of RN from tumor recurrence included relative cerebral blood volume (rCBV) MRI and diffusion weighted imaging (DWI) with associated apparent diffusion coefficient (ADC), demonstrated no restricted diffusion or increased perfusion (Figure 5). Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed focal photopenia with decreased FDG uptake at the site of SRS, consistent with radiation changes (Figure 5). T1 contrast-enhanced MRI at 18 months post-SRS demonstrated a stable, persistently enhancing lesion at the site of SRS (Figure 6). After 4 cycles (2 months) of bevacizumab (20 months post-SRS), T1 axial contrast-enhanced MRI demonstrated minimal enhancement, indicating substantial resolution of the lesion (Figure 7). At 37 months post-SRS, the left thalamic lesion was comparable in size to the MRI at 14 months post-SRS, at which point the patient had become symptomatic (Figure 8).

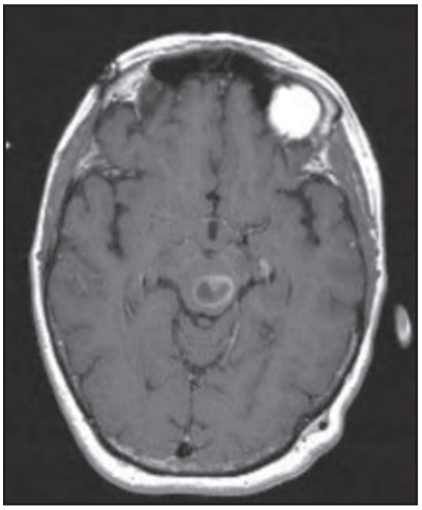

FIGURE 1. *Axial T1 contrast-enhanced MRI demonstrating a 1.8-cm ring-enhancing lesion at the left aspect of the tectum.*

DIAGNOSIS

Differential diagnosis included RN, tumor progression, or mixed RN/tumor progression

DISCUSSION

As reviewed in a previous case study, diagnosing RN is complicated.[1] The only aspect of RN more controversial

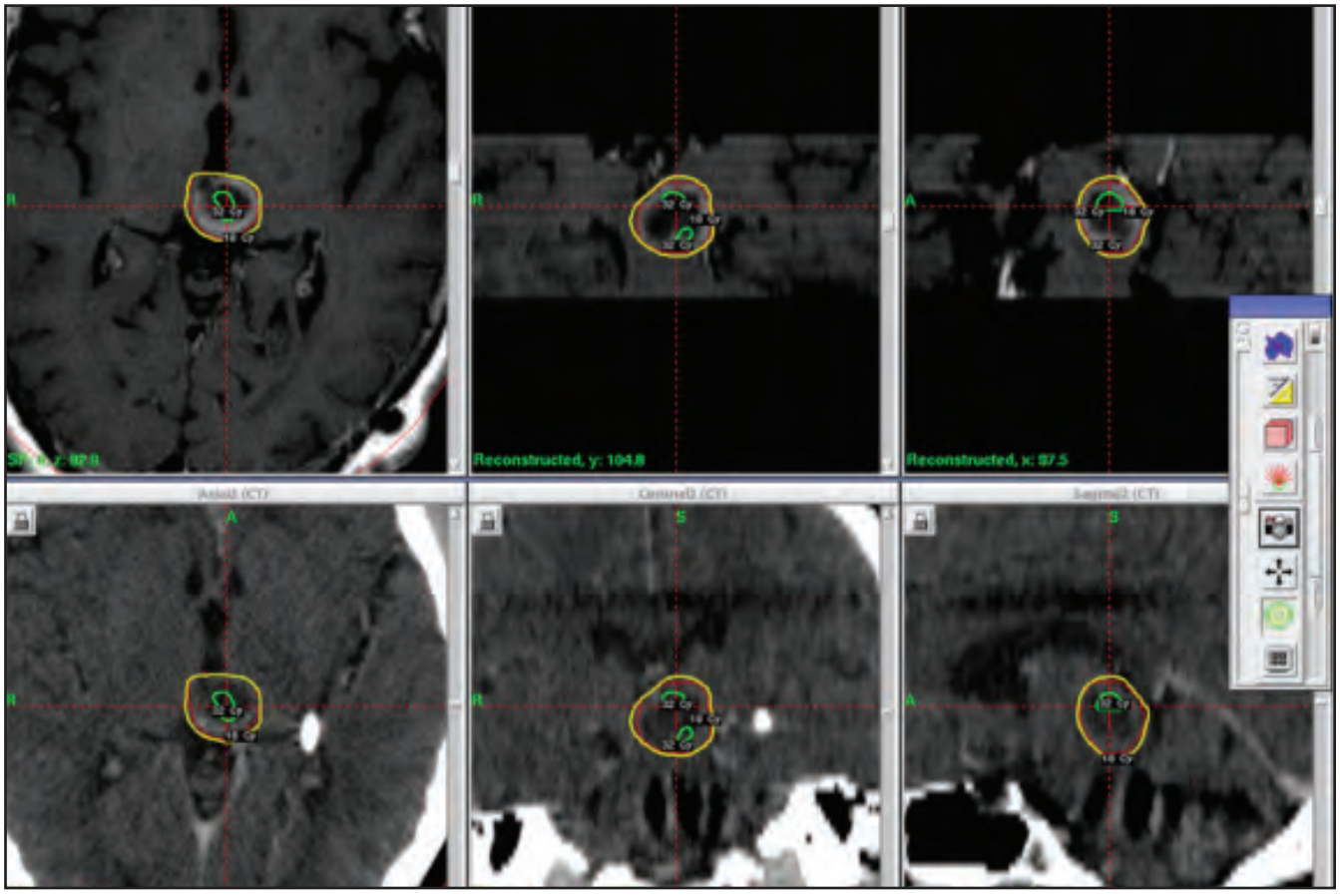

FIGURE 2. *SRS treatment plan for 18 Gy prescribed to the 50% isodose line, which covered 100% of the target. The plan utilized 18 shots using 16-mm, 8-mm, and 4-mm composite sectors. Target volume was 3.9 cm^3. The maximum dose was 36.0 Gy, maximum diameter was 2.1 cm, heterogeneity index (maximum dose/peripheral dose) was 2.000, and conformity index (prescription isodose volume/target volume) was 1.231.*

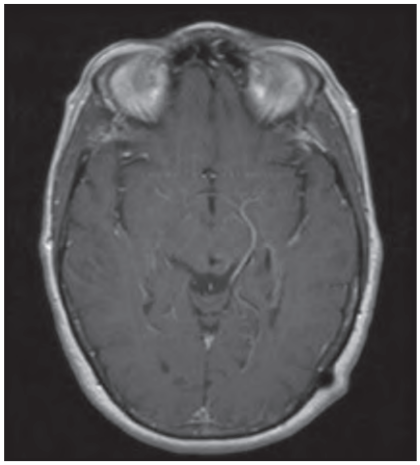

FIGURE 3. *MRI at 12 months post-SRS demonstrated no discrete mass, mass-effect, midline shift or abnormal lesion.*

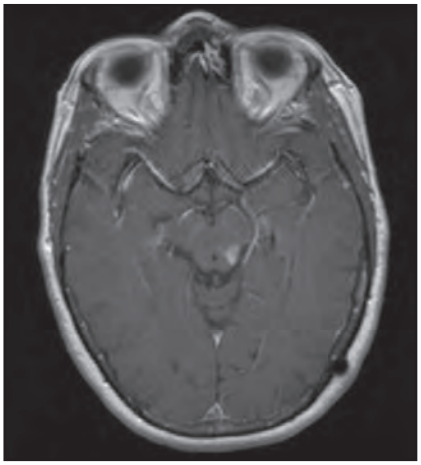

FIGURE 4. *The patient developed symptoms of fatigue and right-sided hemianesthesia, hemithermoanesthesia, and diplopia at 14 months post-SRS. Gadolinium-enhanced T1 axial MRI demonstrated a 0.9 cm x 0.4 cm focus at the site of SRS.*

than accurately diagnosing RN is its management.

Since first discussed in the late 1980s and early 1990s, more than 35 years after pioneering SRS and 60 years after the first case of intracranial RN. In the 30 years since the initial reports, SRS use has increased, but treatment of RN remains nearly as perplexing now as it was then.

Current literature supports the findings of case reports from the 1930s and 1940s, which described clinical courses varying from indolent symptom development to rapidly progressive, fatal courses. Asymptomatic, or radiographic, RN may also occur.

Predictive models and parameters have been developed to reduce the risk of post-SRS RN, but once diagnosed,

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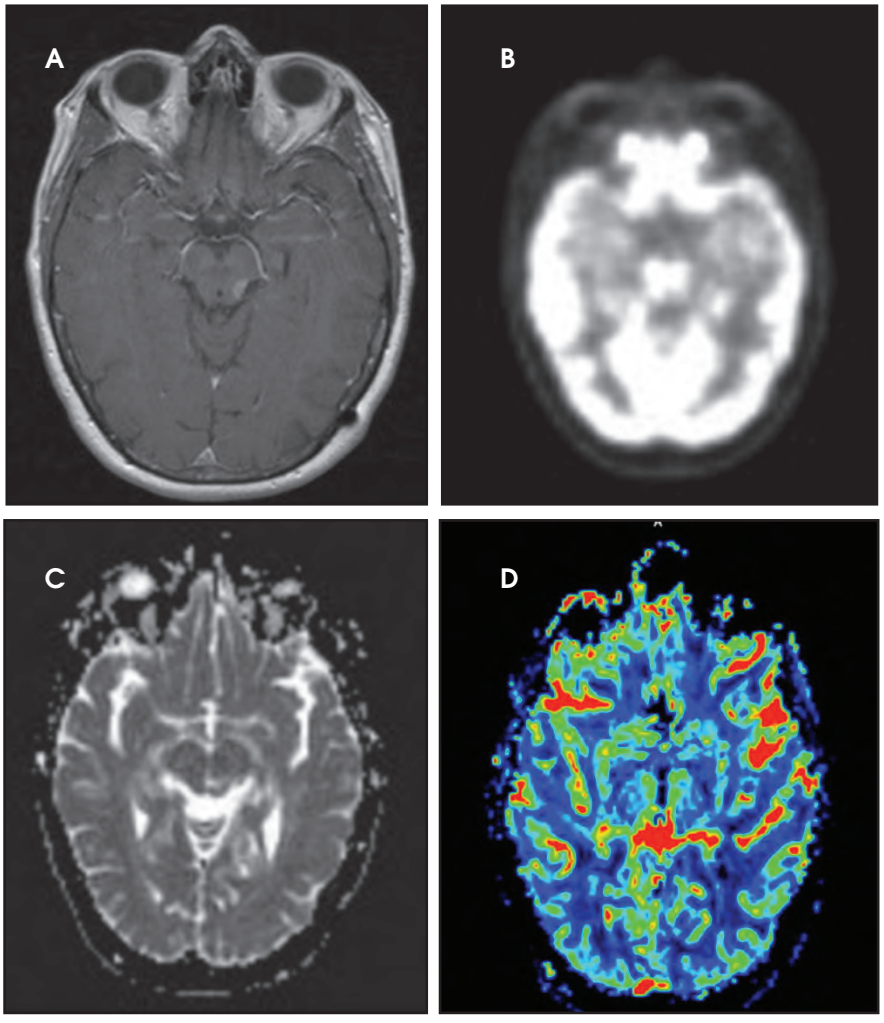

FIGURE 5. *At one month follow up (15 months post-SRS) the lesion was noted to be stable on standard series MRI (A). The treated area was photopenic on FDG-PET (B), demonstrated no decreased diffusion on ADC (C), and was without clear evidence for elevated blood volume in association with this lesion (D). The relative cerebral blood volume assessment was considered to be limited as the left PCA travels in very close proximity to the area of enhancement (within 2 mm) causing substantial increase signal symmetrically about the brainstem related to the arterial enhancement.*

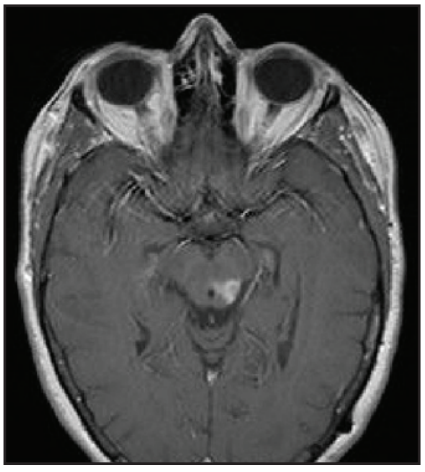

FIGURE 6. *T1W or T1-weighted, contrast-enhanced MRI at 18 months post-SRS demonstrates a stable, enhancing lesion at the site of SRS. Consideration of clinicoradiographic scenario by the multi-disciplinary tumor board yielded recommendation for administration of bevacizumab.*

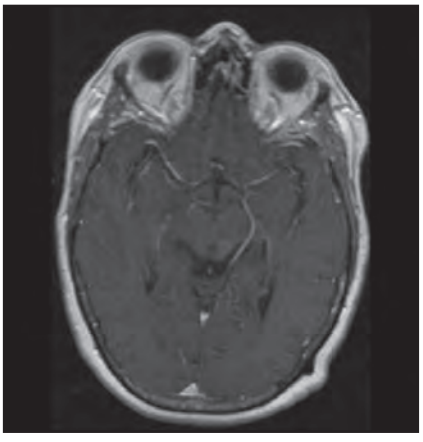

FIGURE 7. *After 4 cycles of bevacizumab (20 months post-SRS, 6 months after onset of new symptoms, and 2 months after commencement of bevacizumab) T1 axial contrast-enhanced MRI demonstrates minimal post-gadolinium enhancement at the site of SRS. No abnormal gadolinium enhancement was noted elsewhere in the brain.*

its treatment remains controversial, as a paucity of data exists regarding RN management.

Published rates of clinical, or symptomatic, RN vary, but may range from 10% to14%. Asymptomatic, or radiographic RN, may occur in 14% to 50% of patients.[1,2] Patients with RN are often treated with corticosteroids, which disrupt the blood-brain barrier, impact VEGF, demonstrate anti-inflammatory effects, and modulate vasodilation, all of which have been linked to the pathophysiology of RN. Patients with RN often demonstrate vasogenic edema, which may result in increased intracranial pressure, focal neurologic symptoms, and seizures. Corticosteroids may bridge these patients through a self-limiting process or they may have therapeutic benefit.[3-5]

Surgery provides histopathologic confirmation and, in many cases, offers sufficient therapeutic intervention. However, not all lesions are amenable to surgical intervention. Non-invasive treatments explored in the treatment of RN include anticoagulation, non-steroidal anti-inflammatory agents (NSAIDs), pentoxifylline with or without vitamin E, bevacizumab, and hyperbaric oxygen therapy (HBOT).

Pentoxifylline with vitamin E was reported in a post-SRS RN case series in which 10 of 11 patients demonstrated

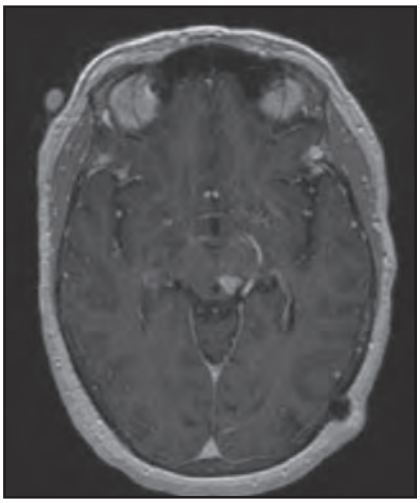

FIGURE 8. *At 37 months post-SRS, the left thalamic lesion has gradually increased in size. At most recent imaging, the lesion was comparable in size to the MRI at 14 months post-SRS, at which point the patient had become symptomatic. Perfusion imaging demonstrates no increase in rCBV.*

volumetric reduction in RN-related edema.[6] The patient without response was subsequently diagnosed with tumor recurrence. No clinical correlation was provided.

One study of 101 brain metastases in 78 patients randomized to post-SRS HBOT demonstrated radiation injury in 11% of HBOT patients and 20% of observation patients.[7] HBOT decreased rates of white matter injury, but not RN incidence.

Bevacizumab (Avastin®) was studied prospectively in a randomized, controlled trial in patients previously treated with fractionated radiotherapy.[8] All patients randomized to bevacizumab, and all cross-over patients, demonstrated clinicoradiographic response to bevacizumab. At 10 months of follow up, 2 of 12 patients analyzed demonstrated radiographic changes consistent with RN recurrence.

Our patient experienced progressive symptoms and radiographic findings despite corticosteroids. Bevacizumab was administered, with dose escalation after 2 cycles for minimal clinicoradiographic response. After 4 cycles, the patient experienced a generalized tonic-clonic seizure and bevacizumab was discontinued. MRI at that time demonstrated resolution of enhancement. Follow-up imaging demonstrated recurrence of enhancement at the site of SRS. The patient currently has persistent, stable radiographic enhancement with right hemianesthesia, right hemithermoanesthesia, and diplopia.

It is unclear whether our patient would have had clinicoradiographic progression without pharmacologic intervention. The lesion may have stabilized after onset of symptoms at 18 months post-SRS. Anecdotal experiences at our institution support case reports denoting varied clinicoradiographic courses of RN.[9,10] Escalation of therapeutic interventions through corticosteroids (without standard "trial" duration), additional pharmacotherapies, HBOT, and surgical intervention is not well established.

The pathogenesis of RN of the brain is not well-understood. No prospective, randomized controlled trials exist regarding post-SRS RN. Interventions remain based on agents effective at mitigating radiation effects in other areas of the body as understanding of post-SRS and its treatment continues to develop.

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