Wanted: Dead or alive? Distinguishing radiation necrosis from tumor progression after stereotactic radiosurgery

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CASE SUMMARY

A 41-year-old woman with a history of melanoma 8 years prior to presenting was diagnosed with a right frontal brain metastasis measuring 1.0 × 1.0 × 0.9 cm (Figure 1). She underwent whole-brain radiotherapy to 37.5 Gy in 15 fractions followed by Gamma Knife stereotactic radiosurgery (SRS) (Figure 2).

The lesion initially regressed, reaching its minimum size 7 months after SRS (Figure 3). Routine imaging at 10 months following SRS demonstrated enlarged contrast enhancement at the treatment site with extension into the left frontal lobe (Figure 4). Despite 2 courses of dexamethasone over 8 months, the lesion enlarged to more than twice its original size (Figure 5). Fluorodeoxyglucose positron emission tomography (FDG-PET), diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC), and perfusion imaging were obtained (Figure 5). The patient was never symptomatic.

Resection of the lesion for diagnosis and management was performed 18 months after SRS. The patient is currently without evidence of active disease 43 months after initial SRS.

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IMAGING FINDINGS

Initial axial T1 contrast-enhanced magnetic resonance imaging (MRI) of the brain demonstrated a 1-cm right frontal lesion (Figure 1) consistent with brain metastasis. At 10 months post-SRS, axial T1 contrast-enhanced MRI showed punctate enhancement, suggesting excellent response to treatment (Figure 3). One month later, axial T1 contrast-enhanced MRI demonstrated interval enlargement of the enhancing area (Figure 4). At 16 months post-SRS, axial T1 contrast-enhanced MRI demonstrated an increase in the size of the treated lesion to more than twice the pretreatment area (Figure 5). Additional imaging was obtained to distinguish radiation necrosis from tumor recurrence. Advanced imaging techniques included relative cerebral blood volume MRI (rCBV) and DWI with associated ADC, which showed no decrease in diffusion (Figure 5). Metabolic imaging with FDG-PET demonstrated focal photopenia with decreased FDG uptake in the anterior right frontal lobe consistent with radiation changes (Figure 5).

DIAGNOSIS

Differential diagnosis included radiation necrosis, tumor progression, or mixed radiation necrosis and tumor progression. Histopathology at the time of resection demonstrated radiation necrosis with no evidence of recurrent tumor (Figure 6).

DISCUSSION

Each year, approximately 170,000 cancer patients develop brain metastases.[1] The current paradigm for treatment of brain metastases often includes SRS, particularly for patients with 3 or fewer lesions all <4 cm, with good performance status.[2] The most serious side effect of SRS is radiation necrosis. Asymptomatic radiation necrosis occurs in an unknown number of patients, but some reports suggest that up to 50% of patients demonstrate radiographic changes consistent with radiation necrosis. Clinical, or symptomatic, radiation necrosis may occur in up to 14% of patients.[3] The duration and severity of symptoms associated with radiation

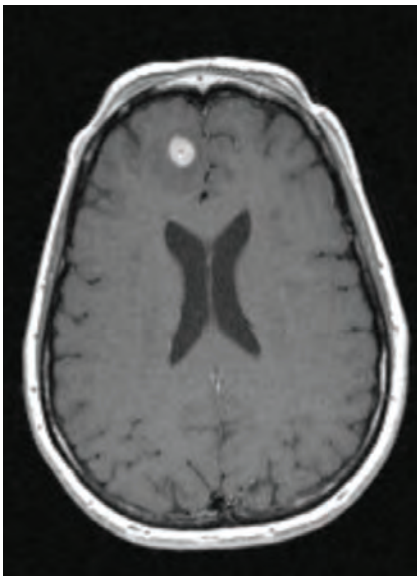

FIGURE 1. *Axial T1 contrast-enhanced MRI demonstrating a single 1-cm ring-enhancing metastasis in the right frontal lobe.*

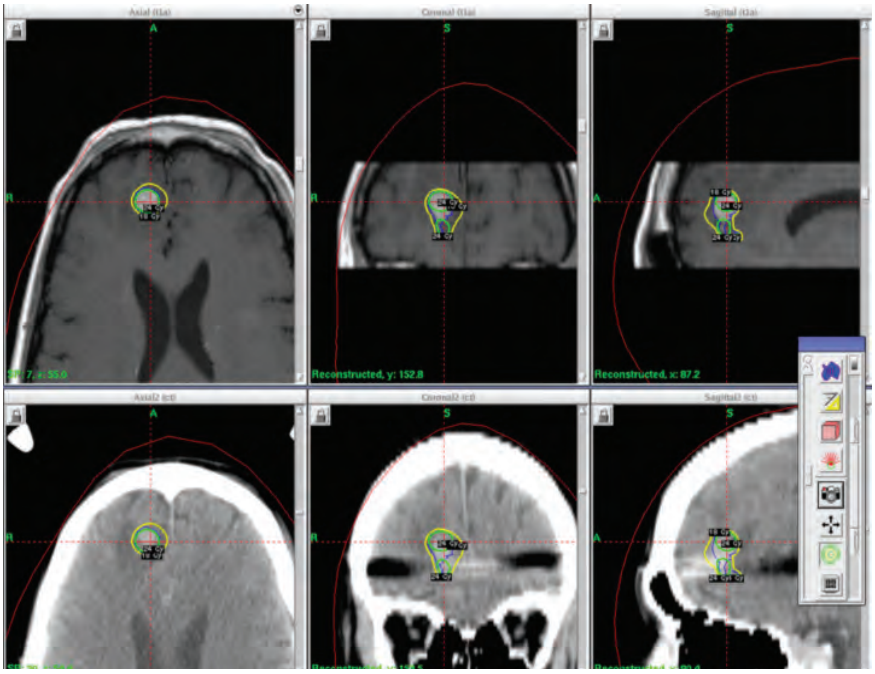

FIGURE 2. *SRS treatment plan for 18 Gy prescribed to the 53% isodose line, which covered 100% of the target. The plan utilized 6 shots using 8-mm and 4-mm helmets, with some of the sectors blocked. Target volume was 1 cm^3. The maximum dose was 34.7 Gy, maximum diameter was 2.4 cm, heterogeneity index (maximum dose/peripheral dose) was 1.928, and conformity index (prescription isodose volume/target volume) was 2.200.*

necrosis vary from a stable, asymptomatic clinical picture of limited duration to a rapidly progressive, lethal course.

The gold standard for diagnosing radiation necrosis is histopathology. To provide an accurate, noninvasive way to distinguish radiation necrosis from tumor progression, standard series MRI scans have been evaluated using characteristic imaging findings, such as "T1/T2 mismatch," or the ratio of the area of a discreet nodule on T2-weighted axial MRI to the area of a discreet nodule on T1 contrast-enhanced axial MRI, with mixed results.[4-6]

Advanced imaging techniques with DWI with ADC mapping, single photon emission computed tomography (SPECT), MR spectroscopy, PET with FDG and other novel radiotracers, and perfusion imaging (perfusion CT and perfusion MRI) have varying degrees of sensitivity and specificity for radiation necrosis and tumor recurrence (Table 1).[6-10] Standard series

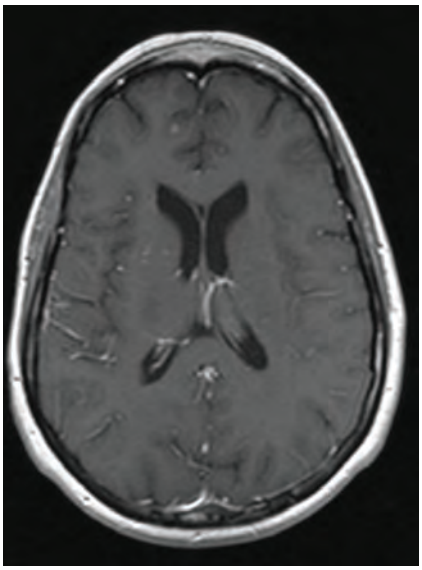

FIGURE 3. *At 10-months, post-SRS the treated right frontal lobe lesion is seen as an area of punctate enhancement in the right frontal lobe.*

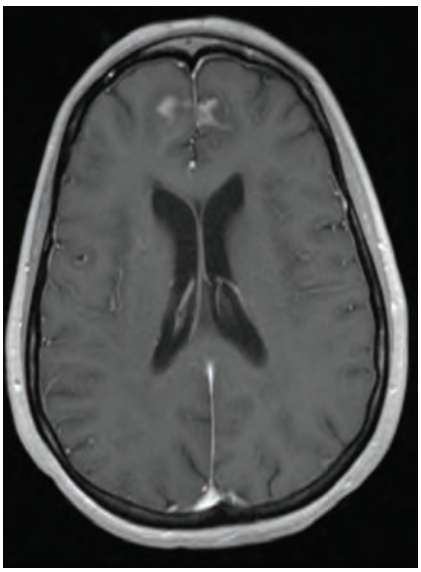

FIGURE 4. *Routine imaging at 11-months post-SRS demonstrated wispy enhancement on this axial T1 contrast-enhanced axial MRI. The patient was started on dexamethasone.*

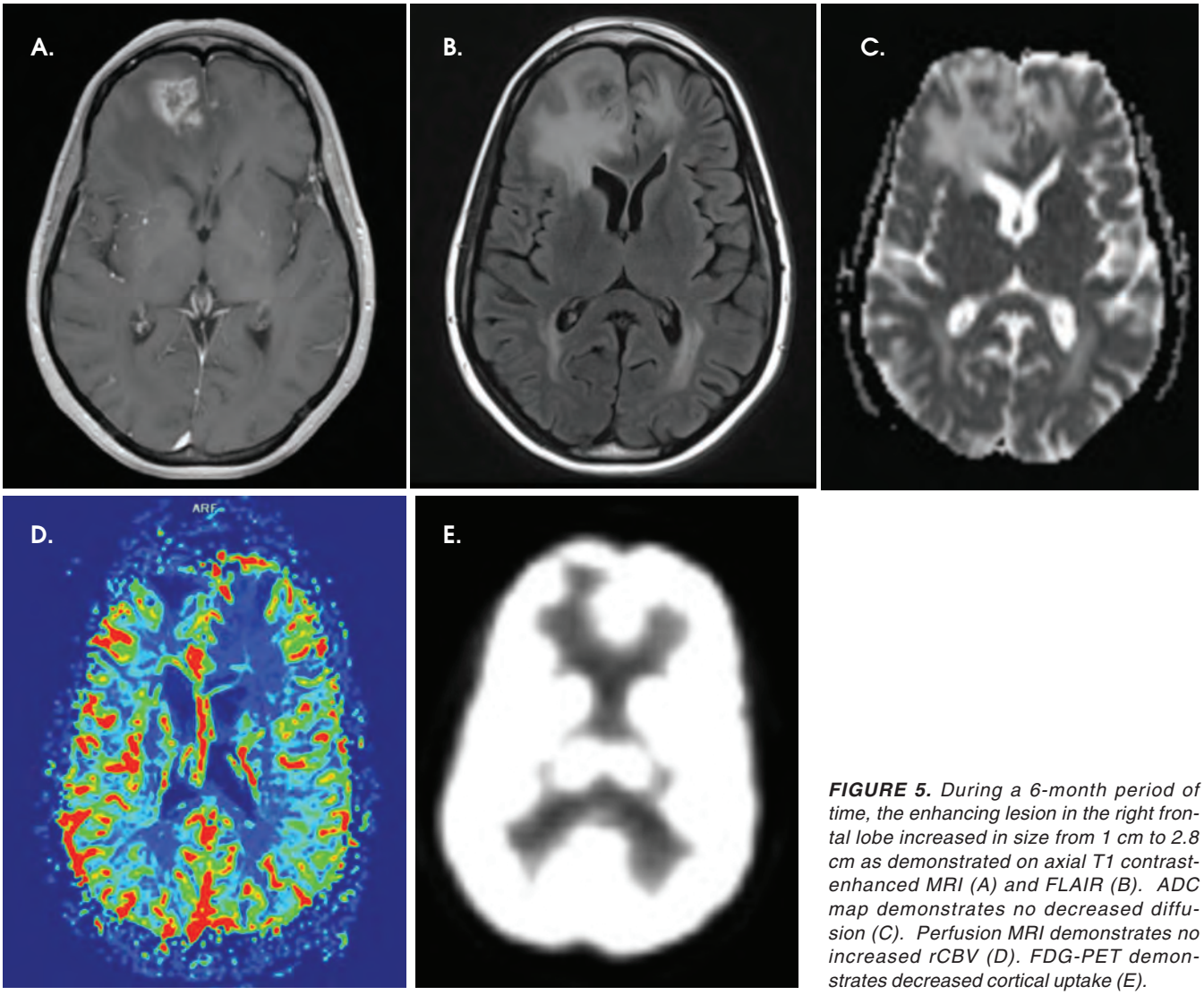

FIGURE 5. *During a 6-month period of time, the enhancing lesion in the right frontal lobe increased in size from 1 cm to 2.8 cm as demonstrated on axial T1 contrast-enhanced MRI (A) and FLAIR (B). ADC map demonstrates no decreased diffusion (C). Perfusion MRI demonstrates no increased rCBV (D). FDG-PET demonstrates decreased cortical uptake (E).*

MRI with perfusion imaging and metabolic imaging with PET are relatively widely available and have relatively high sensitivity and specificity for radiation necrosis and tumor progression. In a small series, multi-voxel MR spectroscopy has demonstrated excellent sensitivity and specificity for tumor recurrence.[3-10]

In our case, the patient was asymptomatic despite an enlarging mass in the context of no increase in rCBV, no decrease in ADC, and a decrease in uptake on PET—all supportive of a diagnosis of radiation necrosis. Histopathology confirmed the suspected diagnosis.

Many times, a patient's radiologic workup will contain some series supportive of radiation necrosis while others support tumor recurrence. Physicians often obtain serial images and consider administering an empiric trial of steroids, as in our case, which may help determine whether the lesion represents radiation necrosis or tumor recurrence. This methodology requires repeated imaging without a defined endpoint.

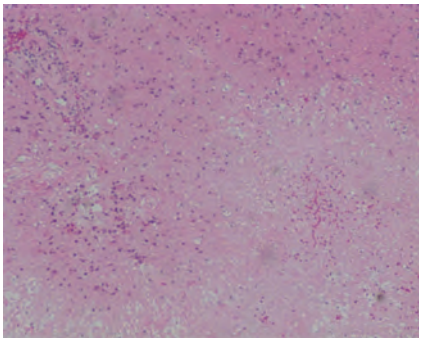

FIGURE 6. *Histopathology demonstrating coagulative necrosis (lower right corner), sclerotic vasculature, and reactive gliosis. No evidence of tumor recurrence was appreciated.*

Table 1. Sensitivity and specificity of imaging modalities utilized in the diagnosis of radiation necrosis and tumor recurrence following SRS for brain metastases

Study	Modality	Necrosis			Recurrence		
		Lesion Quotient	Sensitivity	Specificity	Lesion Quotient	Sensitivity	Specificity
Kano[4]	MRI		84%	91%			
Dequesada[3]	MRI						
		T2/T1 <0.3	80%	96%			
					T2/T1 > 0.6	15%	100%
Stockham[5]	MRI						
		T2/T1 <0.3	8%	91%			
					T2/T1 > 0.6	59%	41%
Chernov[6]	MRS					100%	100%
Chao[7]	FDG-PET (MRI) co-registration					86%	80%
Barajas[8]	PSR Perfusion MRI		96%	100%			
Vidiri[9]	Perfusion CT		72%-86%	100%			
Matsunaga[10]	SPECT				82.8%	83.7%	

MRS = magnetic resonance spectroscopy, FDG-PET = fluorodeoxyglucose positron emission tomography, Met = methionine, PSR = percent signal recovery (associated with perfusion MRI), SPECT = single photon emission computed tomography.

Noninvasive, accurate diagnosis of radiation necrosis versus tumor progression is important, as the clinical course of each can differ widely. In the SRS era, a high index of suspicion for post-SRS radiation necrosis and applying appropriate advanced imaging modalities will aid practitioners in diagnosing radiation necrosis or tumor recurrence, thereby permitting selection of the most appropriate treatment.

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