Radiation necrosis is a known sequela of delivering high doses of ionizing radiation to the central nervous system and may be confused with tumor recurrence. Although stereotactic radiation has found increasing application in managing central nervous system malignancies, the imaging appearance of benign tissue several years after such treatment has not been frequently documented in the medical literature. We present the imaging and pathologic features of brain tissue that received fractionated stereotactic radiation by linear accelerator fourteen years earlier.

Case Report

A 41-year-old woman, previously treated for an intracranial ependymoma fourteen years earlier, presented with the onset of new headaches. She originally presented in 1992 with complaints of right sided headaches; and radiologic evaluation identified a multi-cystic lesion with regions of contrast enhancement in the left posterior parietal region concerning for astrocytoma. After subtotal resection, pathologic evaluation revealed malignant ependymoma with grossly positive margins. Post-operative MRI showed the resection cavity without evidence of gross residual disease. She accepted adjuvant radiation and received fractionated stereotactic radiosurgery with 2700 cGy in six fractions (450 cGy per fraction) to the clinical target volume, followed by 4000 cGy to the brain in twenty fractions (by a wedged pair) with a 600 cGy boost to a reduced volume in three fractions. Treatments were delivered with a 6-MV photon beam for a total clinical target volume dose of 7300 cGy and were completed in June 1992. She tolerated the treatments well and suffered no long-term neurological sequelae. She did not receive chemotherapy.

Between 1992 and 1997, the patient was monitored with regular clinical exams and cranial MRI scans. Her last MRI scan before her re-presentation, in January 1997, showed stable post-treatment changes. There was a small area with minimal high signal on FLAIR sequences with slight vasogenic edema on T2 weighted images, and minimal post-contrast enhancement located adjacent to the surgical tract (Figure 1); this area was thought to be consistent with a cortical venous structure, though tumor recurrence was not entirely excluded.

As she was not experiencing symptoms at the time of her last visit in 1997, the patient elected not to follow-up until early 2006, when she began experiencing right-sided headaches of moderate severity and occasional dizziness. The patient was neurologically intact on physical examination. MRI revealed a large multi-lobulated, partially cystic lesion within the left occipito-parietal region with extensive surrounding vasogenic edema on T2 weighted images and mass effect on the posterior aspect of the left lateral ventricle with minimal midline shift (Figure 2). The solid, enhancing portion of the lesion measured 2.2 cm in greatest dimension, while the entire lesion measured 5.7 cm. The
lesion's cystic components displayed rim enhancement and there was increased cerebral blood volume versus the surrounding brain. No generalized "Swiss cheese" or more isolated "soap bubble" pattern typical of radiation necrosis was identified (1). Together, these findings of new mass effect with midline shift, conspicuous increase of vasogenic edema, and interval development of an enhancing solid lesion with increased blood volume compared with normal tissue were considered to be highly suggestive for tumor recurrence (1, 2).

Resection was undertaken in March 2006. Observed at surgery, the lesion was red in appearance and expressed xanthochromatic fluid when surgically violated. Frozen sections revealed the presence of necrosis and gliosis. Final pathology confirmed the presence of necrosis and gliosis, but no tumor was identified within the resected specimen. The patient returned home, neurologically intact, four days after her surgery, and recovered uneventfully.

Discussion

Cerebral radiation necrosis, an expected late tissue toxicity associated with radiation therapy, has been described as...
Radiation necrosis has varied from 5% to 24% in patients being treated with radiation for malignant gliomas. This wide range among studies has been attributed to different dose and fractionation regimens, improved imaging techniques in modern series, and variable vigilance for this complication across studies. Factors influencing the likelihood of developing cerebral radiation necrosis include: total dose, the volume irradiated, radiation fraction size, addition of concurrent chemotherapy, survival time of the patient, age of the patient at time of treatment, biologic equivalent dose (BED in Gy2), and the product of dose and fraction size (Gy2)(1, 3, 6). A recent retrospective study by Ruben et al. looked at radiation necrosis incidence for 352 patients that received a BED greater than or equal to 85.5 Gy2 (equivalent to 45 Gy in 25 fractions using an alpha/beta ratio of 2 for brain tissue) for treatment of gliomas. This group identified a mean interval of 11.6 months from the end of radiation to the identification of necrosis and a greater than four-fold increase in risk of necrosis with the use of concurrent chemotherapy (6). The

Figure 2A. Fourteen years after treatment for malignant ependymoma, axial FLAIR MRI image showed development of a partially cystic lesion within the left occipital-parietal region with extensive edema, mass effect on the left lateral ventricle, and midline shift.

Figure 2B. Fourteen years after treatment for malignant ependymoma, axial T2-weighted MRI showed development of a partially cystic lesion within the left occipital-parietal region with extensive edema, mass effect on the left lateral ventricle, and midline shift.

Figure 2C. Fourteen years after treatment for malignant ependymoma, axial post-gadolinium FLAIR MRI image showed a new multi-cystic lesion with a prominent solid component displaying marked contrast enhancement.
Radiation Necrosis Masquerading as Late Tumor Recurrence

total dose of radiation was the most important factor for development of subsequent necrosis, and no instances of radiation necrosis were identified at a BED less than 96Gy2. The patient in our case received a BED of 180Gy2.

Differentiating tumor recurrence from radiation-induced necrosis after high dose radiation therapy for a brain tumor by imaging can be challenging. This difficulty may be compounded in patients that have undergone radiation dose escalation by stereotactic techniques since the long-term appearance and evolution of damage to normal intracranial tissues thus treated has been incompletely characterized in the published literature. Diffuse radiation necrosis after conventional radiation techniques typically gives areas of increased signal intensity on T2-weighted and FLAIR sequences, often in a periventricular distribution (3). There is debate as to which, if any, individual conventional MRI features are most consistent with necrosis. Kumar et al. identified both a diffuse “Swiss cheese” and the more isolated "soap bubble" patterns as characteristic of necrosis (1), while Mullins et al. (looking at patients treated with proton beams) found that individual imaging features were unable to reliably differentiate tumor recurrence from necrosis (4). Rather, Mullins et al. showed that combinations of findings may be most useful in identifying progressive glioma (e.g. corpus callosum involvement with multiple enhancing foci) (4). Perfusion-sensitive MRI allows for non-invasive evaluation of the passage of blood through the brain's vasculature by measuring cerebral blood volume, blood flow, and/or mean transit time; a significant increase in perfusion relative to normal tissue is considered highly suggestive of malignancy (3). As shown in our case, MRI findings normally suggestive of recurrent disease such as new mass effect with midline shift, conspicuous increase in vasogenic edema, increase in cerebral blood volume versus the surrounding brain, and development of an enhancing solid lesion may be misleading (2, 3). We recommend a continued vigilant approach to the follow-up of patients treated with stereotactic radiation therapy with the awareness that the radiographic appearance within the high dose regions can be protean. Research into more accurate delineation of tumor recurrence from benign tissue damage after conformal application of high doses of radiation is ongoing (3, 4).

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