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Teaching Case

Recurrent radiation necrosis in the brain following stereotactic radiosurgery

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Case presentation

A 72-year-old woman with newly diagnosed metastatic non–small cell lung cancer (NSCLC) presented with 3 asymptomatic brain metastases on staging magnetic resonance imaging (MRI), including a 2.1-cm left parietal cystic metastasis (Fig 1A) and 2 sub-centimeter metastases. She had no significant past medical history or prior history of radiation therapy. She received stereotactic radiosurgery (SRS) to all 3 metastases, including 18 Gy in 1 fraction to the left parietal metastasis (Fig 1B). One week later, she began erlotinib because her adenocarcinoma harbored an epidermal growth factor receptor (EGFR) mutation. Two months after SRS, an MRI scan revealed minimal increase in size and edema surrounding all 3 lesions, and she remained asymptomatic.

Four months after SRS, the patient experienced a right hand/leg focal seizure, with word-finding difficulty. MRI revealed enlargement of the left parietal metastasis with increased edema (Fig 1C). Dexamethasone was initiated with a 3-week taper, plus levetiracetam. She improved initially, but because of ongoing motor seizures, she was

offered surgery for the left parietal metastasis, with suspicion for tumor progression versus radiation necrosis. Preoperative brain positron emission tomography computed tomography or magnetic resonance spectroscopy was not performed because of the predominantly cystic nature of the lesion. Left parietal craniotomy was performed (5 months after SRS treatment), revealing firm, nonviable tissue surrounding a fluid cavity. All abnormal tissue was completely removed. Pathologic examination revealed necrotic tissue (radiation necrosis) with scattered calcifications and hemosiderin deposits as well as adjacent viable gliotic brain tissue (Fig 2). There was no evidence of residual NSCLC. The patient received a slow dexamethasone taper following surgery, and she resumed erlotinib 1 week after surgery. Six weeks after surgery, she was clinically stable and MRI showed decreased enhancement and edema (Fig 3A).

Six months after surgery, the patient reported recurrent right hand/leg focal motor seizures. She had been receiving erlotinib monotherapy without chemotherapy. MRI revealed nodular enhancement of the left parietal cavity, and worsened edema (Fig 3B, C). Repeat left parietal craniotomy was performed (6 months after the first craniotomy) given the high suspicion for local tumor recurrence, with a markedly firm, nonviable mass noted intraoperatively, which was totally removed. Surprisingly, microscopic examination revealed no evidence of recurrent NSCLC.
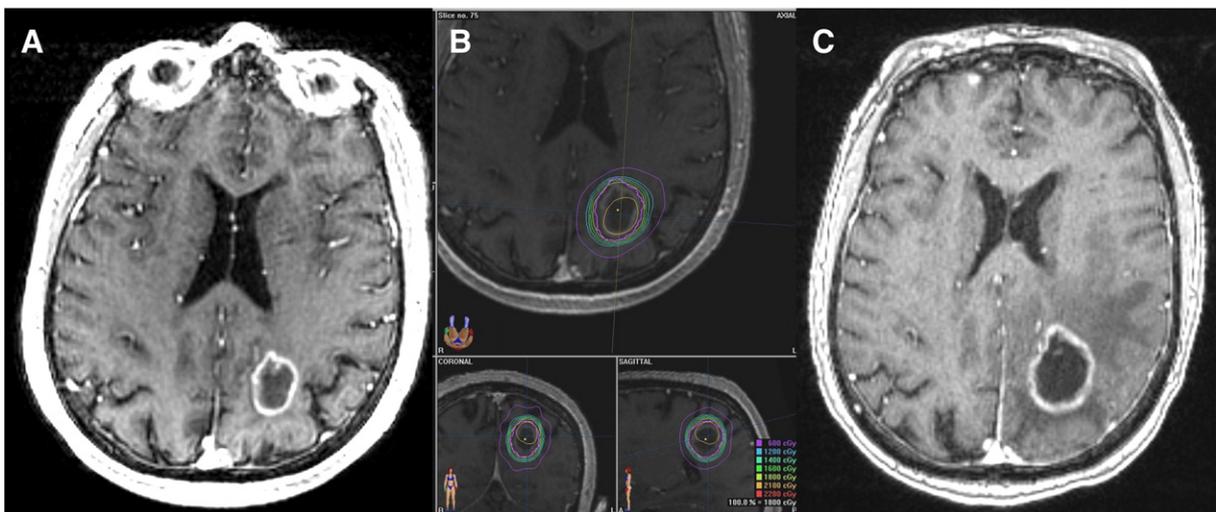
Figure 1 (A) Magnetic resonance imaging (MRI) revealed a 2.1-cm left parietal cystic metatsasis with vasogenic edema. (B) Stereotactic radiosurgery (SRS) plan for 18 Gy in 1 fraction, target volume of 7.5 mL, with conformity index of 1.30. (C) Four months after SRS treatment, MRI revealed an increase in size and surrounding edema.
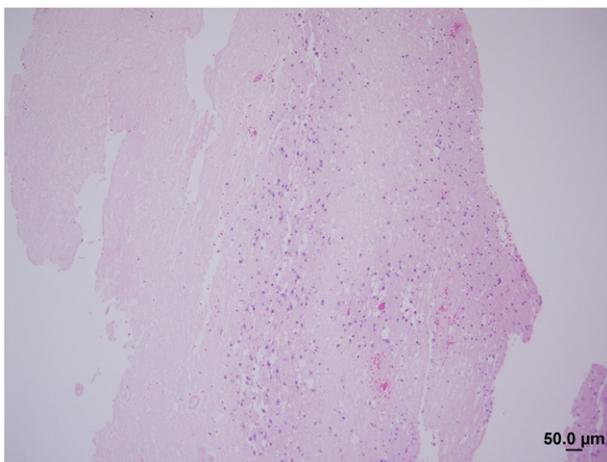
The resected material contained areas of necrosis and fragments of reactive brain tissue with neovascularization, prominent macrophage infiltrates, and scattered chronic inflammatory cells (Fig 4A, B), consistent with radiation necrosis. Immunohistochemistry for vascular endothelial growth factor expression (VEGF; Fig 4C, D) showed diffuse strong cytoplasmic staining in reactive brain tissues compared with adjacent normal brain parenchyma (Fig 4E). Two months postoperatively, she had clinically improved, and MRI revealed decreased size of the left parietal cavity, and she resumed erlotinib. One year following the second surgery, she is clinically stable with rare breakthrough focal motor seizures, and MRI scans remain stable. Of note, her 2 smaller brain metastases that received SRS at the time of

Figure 2 Hematoxylin and eosin–stained section of the resected left parietal metastasis (5 months after SRS) revealed necrotic tissue consistent with radiation necrosis and scattered foci of reactive brain tissue, with no residual non–small cell lung cancer.

initial diagnosis showed radiographic decrease in size and eventual stability on all follow-up scans after her initial post-SRS MRI.

Discussion

This case reveals pathologically proven brain radiation necrosis following SRS that recurred despite complete surgical resection 6 months earlier, without additional radiation therapy being delivered in the interim between surgeries. The development of radiation necrosis as a late complication of SRS is well-known.[1] However, diagnostic challenges make determination of the true incidence of radiation necrosis difficult, with estimates ranging from 5% to 25% following SRS, with most studies reporting rates <10%.[2,3] Radiation necrosis typically appears on MRI as an increase in lesion enhancement suggesting blood–brain barrier disruption, plus surrounding edema, often occurring at least 6–12 months following SRS treatment. This mimics tumor recurrence, and thus conventional MRI is unreliable in the diagnosis of radiation necrosis after SRS. Alternative neuroimaging approaches to distinguish between tumor recurrence and necrosis have been investigated,[1] yet the distinction between the 2 entities remains a challenge. Ultimately, histopathologic examination remains the gold-standard diagnostic method. To our knowledge, this is the first report of pathologically confirmed radiation necrosis following SRS that recurred after complete surgical resection and highlights important diagnostic considerations for patients being followed after SRS.

There are several proposed risk factors for radiation necrosis, including radiation dose, fraction size, volume
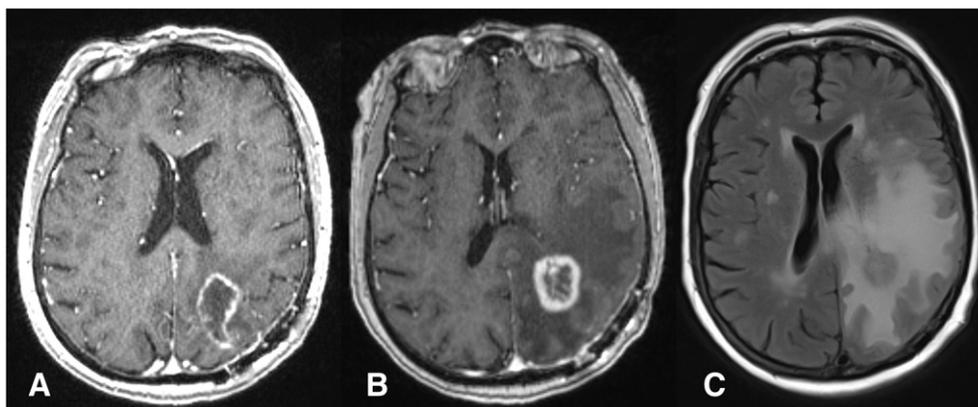
Figure 3 (A) Postoperative magnetic resonance imaging (MRI) of the left parietal cavity with partial collapse and decreased edema. Six months after the first craniotomy, MRI showed (B) progressive nodular enhancement of the cavity (T1 postcontrast) and (C) worsened edema (T2/fluid attenuated inversion recovery).

treated, chemotherapy, and prior irradiation.[1] Studies suggest the risk of radiation necrosis following SRS for brain metastases may be at least 50% when the volume of normal brain receiving ≥ 12 Gy exceeds 10 mL.[4] In our case, the volume of normal brain receiving ≥ 12 Gy was associated with the left parietal target was 8.9 mL. In addition, our patient had an EGFR-mutant NSCLC and was receiving erlotinib, a tyrosine kinase inhibitor known to penetrate the blood–brain barrier.[5] This raises the possibility that erlotinib sensitized the tumor bed and surrounding brain tissue to radiation injury, which has been reported in the setting of other molecularly targeted therapies, including vemurafenib[6] and trastuzumab[7] after

brain radiation therapy. Specifically, EGFR-mutant NSCLC has shown increased radiosensitivity relative to wild-type EGFR NSCLC,[8] and thus the tumor cells may have been radiosensitized through receipt of erlotinib. Additionally, erlotinib has been associated with various forms of radiation recall phenomena in non-dermatologic settings,[9,10] and in this case erlotinib may have exacerbated the surrounding normal brain tissue's inflammatory response causing radiation necrosis as a form of radiation recall.

The mechanism of radiation necrosis is incompletely understood but appears related to ionizing radiation damage of endothelial cells leading to tissue hypoxia and
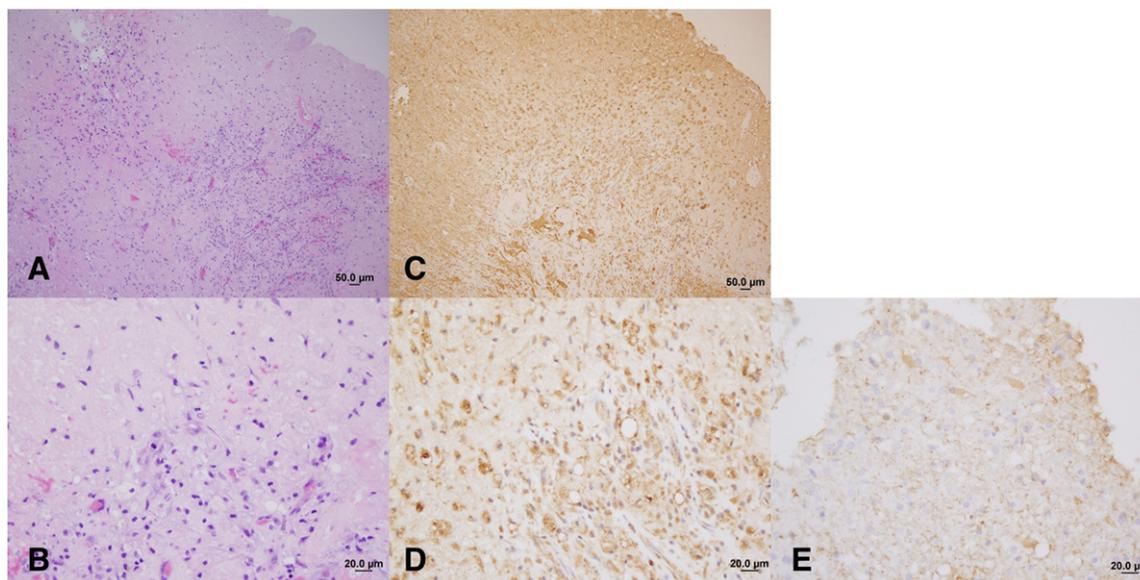
Figure 4 Microscopic findings after repeat left parietal craniotomy, 6 months after the initial craniotomy. (A) Hematoxylin and eosin examination revealed global regions of radiation necrosis and gliotic brain tissue with neovascularization and chronic inflammatory infiltrates. (B) Region of neovascularization, including hyalinized vessels, in background of reactive brain tissue. (C) Vascular endothelial growth factor (VEGF) immunohistochemical (IHC) stain demonstrating diffuse expression. (D) VEGF IHC highlighting cytoplasmic protein expression in blood vessels, reactive glial cells, and macrophages. (E) VEGF IHC staining of adjacent normal brain tissue distant from the region of radiation necrosis, showing basal low level of VEGF expression.

fibrinoid necrosis of small arteries, with demyelination of neurons, mediated by various cytokines.[11] Studies suggest a role for VEGF, based on increased tissue expression of VEGF after radiation injury in the central nervous system, particularly in the perinecrotic region.[12] Therapy with bevacizumab, an antibody against VEGF factor A, has been shown in a small randomized trial to improve neurologic symptoms and radiographic appearance in patients with brain radiation necrosis.[13] For our patient, bevacizumab therapy may be considered if the left parietal lesion enlarges or symptoms return in the future. The mechanism for this patient's recurrent radiation necrosis is unclear, but may have been triggered by persistent inflammatory and/or vasoactive mediators including VEGF within the unresected, normal-appearing brain parenchyma adjacent to the surgical cavity, along with continued receipt of erlotinib. Besides bevacizumab, an emerging therapeutic modality for radiation necrosis in the brain is laser interstitial thermal therapy, which uses thermocoagulation to destroy inflammatory cellular infiltrate in the region of necrosis, with a small but growing evidence base.[14] This case highlights the ongoing risk of late brain complications after SRS because patients are living longer on improved systemic therapies and is a diagnostic consideration for physicians monitoring patients after SRS.

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