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Case Report

Co-Occurrence Conundrum: Brain Metastases from Lung Adenocarcinoma, Radiation Necrosis, and Gliosarcoma

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Abstract
Non-small cell lung cancer (NSCLC) commonly presents with metastasis to the brain. When brain metastases are treated with stereotactic radiosurgery (SRS), longitudinal imaging to monitor treatment response may identify radiation necrosis, metastasis progression, and/or another primary brain malignancy. A 60-year-old female with metastatic NSCLC involving the brain underwent treatment with systemic therapy and SRS. While some brain metastases resolved, two remaining sites evolved to resemble radiation necrosis on magnetic resonance imaging and spectroscopy. One of those sites was later confirmed to be radiation necrosis after receding with steroids and bevacizumab. The other lesion continued to enlarge and was then surgically resected, pathologically proven to be a gliosarcoma. When scan findings diverge among multiple treated disease sites, imaging should be cautiously interpreted in conjunction with clinical information as well as early surgical consultation for biopsy consideration, especially when there is suspicion of unusual or superimposed pathologies.

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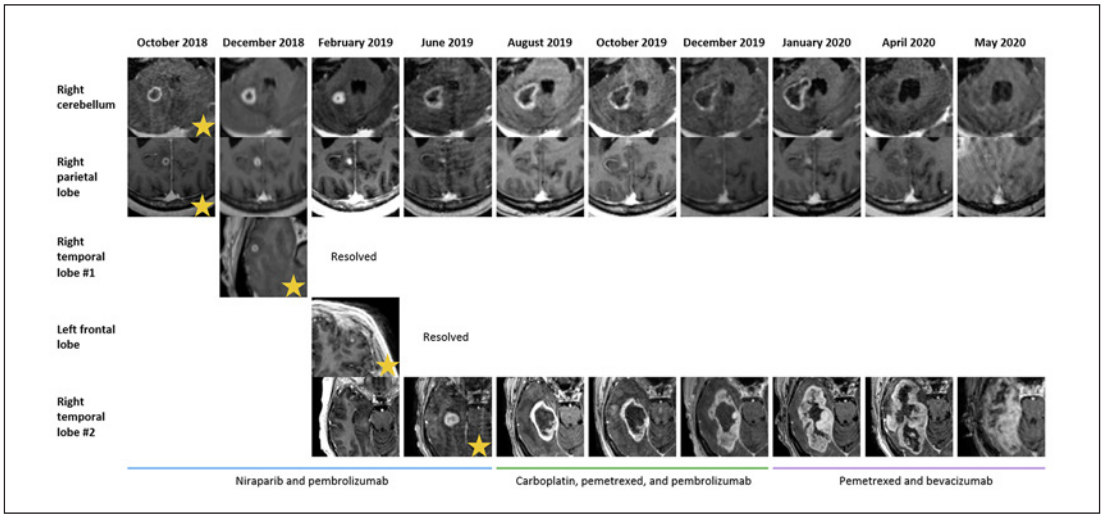

Fig. 1. Serial MRI scans. Timeline of systemic therapies and MRI scan findings, stratified by brain lesion sites. Yellow stars denote treatment by stereotactic radiosurgery at a corresponding time point and lesion.

Introduction

Non-small cell lung cancer (NSCLC) is the most common source of metastases to the brain. With improving systemic therapies that prolong survival, brain metastasis (BM) incidence is rising and estimated to develop in up to half of all patients with NSCLC [1]. Stereotactic radiosurgery (SRS) has become the most popular approach for treating BMs in patients with good performance status and a limited number of BMs. However, due to vascular injury and local inflammation induced by SRS, about 10% of patients experience the complication of radiation necrosis months to years following treatment, with an increasing trend that is related to the growing use of immunotherapies [2].

One challenge of managing radiation necrosis is its radiographic resemblance to tumor progression. The rare chance of having a co-occurring primary brain malignancy further convolutes proper workup. To our knowledge, we present the first unusual report of a patient with synchronous NSCLC metastatic progression in the brain, radiation necrosis following SRS treatment, and a gliosarcoma.

Case Presentation

In October 2018, a 60-year-old female with over 30 pack-years of smoking history presented with 3 weeks of worsening posterior headache, right upper extremity dysmetria, truncal ataxia, and no nausea. Imaging detected lesions in the right cerebellum (1.1 cm), right parietal lobe (0.6 cm), and right upper lobe of the lung (2.8 cm). Paratracheal nodal biopsy established the diagnosis of metastatic lung adenocarcinoma (*KRAS* G12C+ and PD-L1 > 50%).

Her two BMs were treated with SRS, and she was started on a phase 2 trial of niraparib plus pembrolizumab. Between December 2018 and June 2019, she received additional SRS for new lesions (Fig. 1), including a second right temporal lobe lesion just medial to the first. In July 2019, she came off trial for disease progression and was started on carboplatin, pemetrexed, and pembrolizumab. From August to December 2019, headache

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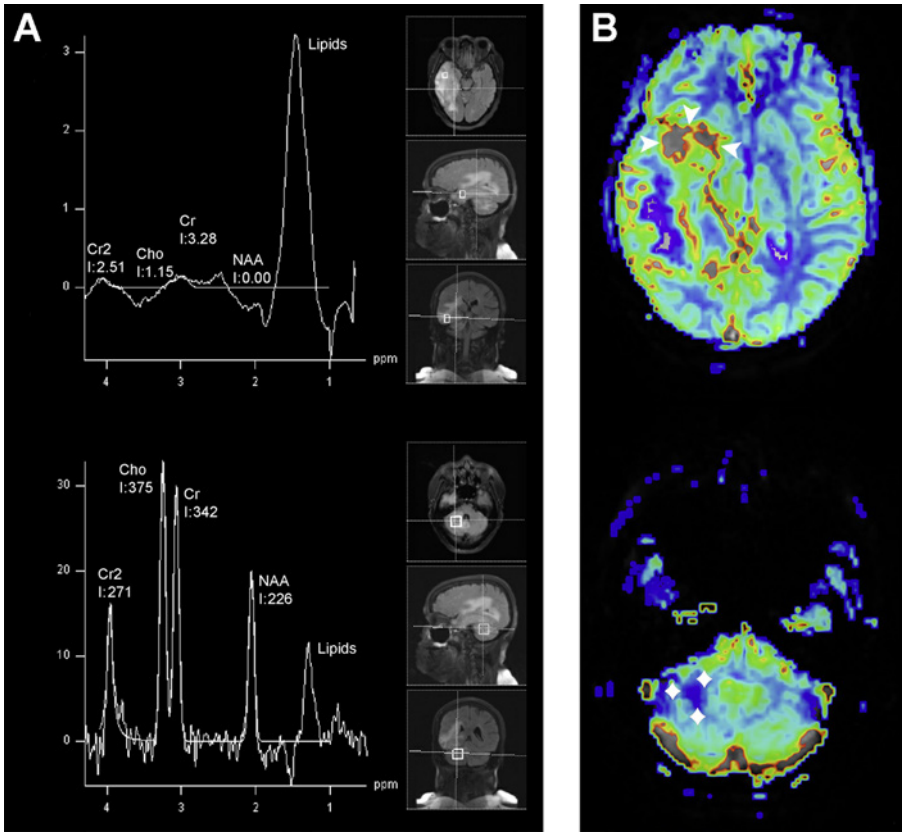

Fig. 2. Advanced MRI sequences. **A** Representative magnetic resonance spectra of metabolites in voxels of the right temporal lobe (top) and right cerebellum (bottom) in December 2019. **B** Dynamic susceptibility contrast magnetic resonance perfusion imaging of the right temporal lobe (top, hyperperfusion outlined by white arrowheads) and right cerebellum (bottom, hypoperfusion outlined by white diamonds) in April 2020.

worsened. Despite steroid therapy for presumed radiation necrosis, MRI showed expansion of the peripheral enhancing lesions in the right temporal lobe and right cerebellum. MR spectroscopy in December 2019 depicted lipid abundance, favoring necrosis over tumor at both lesions (Fig. 2A). The primary lung mass and mediastinal lymphadenopathy receded through 2019. Systemic therapy was switched to pemetrexed and bevacizumab to continue treatment of metastatic NSCLC while escalating intervention for likely radiation necrosis.

From January to May 2020, this patient developed new right hand tremor, blurry vision, dysarthria, and personality change. The right cerebellar lesion then improved along with resolution of right hand tremor, whereas the right temporal lobe lesion further enlarged on bevacizumab and steroids. MRI with perfusion in April 2020 displayed hyperperfusion in the right temporal lobe, but not in the right cerebellum (Fig. 2B). She was then hospitalized for altered mental status and underwent decompressive resection of the right temporal brain mass. Pathology revealed gliosarcoma (*IDH*-wild type, *MGMT* promoter methylated) without evidence of metastatic carcinoma (Fig. 3). Baseline alertness and orientation returned after surgery. Headache also improved, but dysarthria and labile affect persisted. Her overall performance status was deemed appropriate for hypofractionated adjuvant chemoradiation. She underwent CT simulation for radiotherapy planning without difficulty, however became progressively more agitated during setup for daily radiation delivery such that accurate

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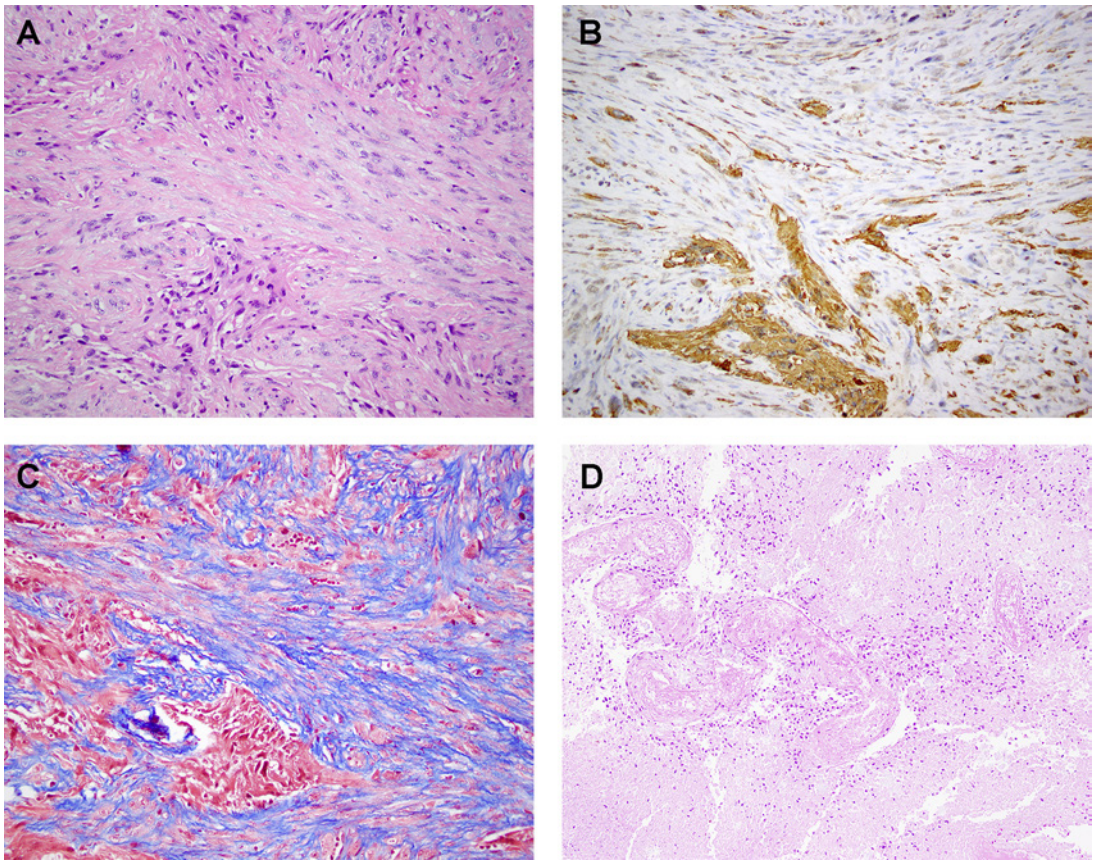

Fig. 3. Histopathologic assessment of the right temporal lobe lesion. **A** Hematoxylin and eosin (H&E) stained specimen showing an admixture of tumor cells with astrocytic and spindled morphology (magnification, ×20). **B** Positive immunostain for GFAP (brown), consistent with glial cells (magnification, ×20). **C** Positive Masson trichrome stain for abundant collagen deposition (blue), a feature of sarcomatous cells (magnification, ×20). **D** H&E stained specimen showing necrosis with viable perivascular tumor cells, more characteristic of tumor necrosis than radiation-associated necrosis (magnification, ×10).

targeting could no longer be ensured. Following thorough discussion of the risks and benefits of continuing treatment with the patient and family members, she agreed to home hospice and was discharged from the hospital.

Discussion and Conclusion

Discernment of tumor progression from radiation necrosis was complicated by several factors. Patients on immune checkpoint inhibition (ICI) or targeted therapy are significantly more likely to experience radiation necrosis following SRS, up to 38 and 25%, respectively, compared to those on chemotherapy (17%) [3] or no systemic therapy (7%) [2]. This patient received both ICI and targeted therapy. Regarding her second right temporal lobe lesion, its rate of growth, initial eccentric leading edge, peripheral and nodular enhancement extending into the necrotic zone, and asymptomatic manifestation all support early presumption of radiation necrosis [4]. However, rapid emergence after SRS argues against radiation necrosis. Presence of small satellite nodules also argues against metastatic progression.

MR spectroscopy demonstrated prominent lipid peaks suggestive of necrosis without significant elevation of choline-to-creatinine or choline-to-*N*-acetylaspartate ratios suggestive of tumor growth [5], in both the right temporal lobe and cerebellar lesions. In retrospect, the differential diagnosis could have been expanded at this point to include malignancies typified by extensive necrosis such as high-grade glioma, instead of remaining focused on metastatic carcinoma and radiation necrosis. Response of the right cerebellar lesion to bevacizumab added evidence in favor of radiation necrosis, but the right temporal lesion did not evolve in parallel. Multidisciplinary discussion ultimately reached consensus that the right temporal lesion was likely to be neither metastatic NSCLC given disease regression elsewhere, nor radiation necrosis given the lesion's aggressive growth through steroids and bevacizumab. A more easily accessible lesion would have likely prompted an earlier biopsy. In this case, surgical intervention was deferred until acute neurologic changes occurred.

Radiation necrosis is expected to become increasingly common due to cancer patients with BMs living longer and receiving combination treatments that involve SRS and ICI. Advanced MR sequences including spectroscopy (sensitivity 36–94%, specificity 55–100%) and perfusion (sensitivity 50–96%, specificity 70–100%) [5] should be invoked to better distinguish tumor progression from radiation necrosis in equivocal cases. Unfortunately, these advanced techniques also have limitations and may convey misleading impressions, particularly if interpreted in isolation. In cases like this when imaging findings diverge among multiple treated lesions, conventional and advanced imaging should be interpreted by an experienced multidisciplinary team in conjunction with clinical information, such as unresponsiveness to anti-neoplastic therapies, steroids, and bevacizumab. In exceptionally confounding cases, neurosurgical consultation for biopsy should be considered, and tissue sampling may ultimately be required to make an unusual or superimposed diagnosis.

Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and its accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

D.C.Q.: study design, writing the manuscript, acquisition and interpretation of data, and review and revision of the manuscript. B.D.W.: writing the manuscript, interpretation of imaging, and review and revision of the manuscript. S.G.N., A.L.G.: writing the manuscript, interpretation of pathology, and review and revision of the manuscript. J.J.O., A.D.V., S.S.R.:

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