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Basal ganglia glioblastoma with lung adenocarcinoma tumor-to-tumor metastasis and atypical early imaging presentation: illustrative case

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BACKGROUND Tumor-to-tumor metastasis is a rare oncological phenomenon in which one neoplasm serves as the recipient for metastatic seeding from another primary tumor. Glioblastoma is an exceptionally uncommon recipient, and no prior reports have described this process occurring in the setting of atypical early imaging presentation.

OBSERVATIONS The authors present an unusual case of a 75-year-old man with hemiplegia and hemianesthesia with initial brain imaging demonstrating a solitary right basal ganglia diffusion-restricting, nonenhancing lesion initially diagnosed as a subacute ischemic stroke. Follow-up imaging triggered by progression of patient's weakness revealed rapid lesion enlargement and new contrast enhancement. Stereotactic biopsy demonstrated features of both high-grade glioma and metastatic pulmonary adenocarcinoma. Subsequent molecular profiling confirmed glioblastoma, *IDH*-wildtype (CNS WHO grade 4) and concurrent metastatic pulmonary adenocarcinoma. Despite whole-brain radiation therapy, the patient's condition rapidly deteriorated.

LESSONS This case highlights the importance of maintaining diagnostic suspicion for dual pathology in atypical intracranial lesions with progressive, otherwise unexplained symptoms. Furthermore, this case highlights the challenges in recognizing early glioblastoma presenting with nonenhancing, diffusion-restricting imaging features that may closely mimic subacute ischemic stroke. The integration of histopathology, immunochemistry, and molecular profiling is critical in recognizing this entity and carries significant implications for accurate diagnosis and treatment.

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KEYWORDS collision tumor; glioblastoma; lung adenocarcinoma; tumor-to-tumor metastasis

Tumor-to-tumor metastasis is a rare oncological phenomenon in which one neoplasm serves as the recipient of metastatic seeding from another primary malignancy. For definitive diagnosis, certain criteria must be met, as described by Campbell et al.: 1) two primary tumors must exist, 2) the recipient tumor must be a true neoplasm, 3) metastasis should not be the result of contiguous growth or tumor embolization, and 4) neoplasms that have metastasized to the lymphatic system where lymphoreticular tumors already exist are excluded.[1] These principles help differentiate tumor-to-tumor metastasis from collision tumors that are defined by two adjacent histologically distinct tumors with contiguous growth into one another.[2,3] Because of their growth pattern, they violate the third principle described by Campbell et al. and are recognized as a separate entity.

Given the complexity of these processes, distinguishing true tumor-to-tumor metastasis remains diagnostically challenging. Among the reported cases, the combination of glioblastoma and metastatic carcinoma represents one of the least frequently encountered entities in neuro-oncology.[3,4] Since the first documented case of carcinoma metastasizing into a malignant glioma in 1960,[3,5] fewer than 20 cases have been reported in the literature, with only 3 of those being in glioblastoma patients.[3,5,6] However, careful review of the literature suggests that 2 of these 3 cases likely represent alternative diagnostic entities. To our knowledge, only one prior case of true tumor-to-tumor metastasis into glioblastoma has been convincingly documented.[3] Notably, there has never been a documented case of this phenomenon occurring in the setting of atypical early imaging presentation of glioblastoma characterized by isolated diffusion restriction without enhancement. In this report, we discuss the potential pathophysiological mechanisms involving both the donor and recipient malignancies, the implications of early, nonenhancing diffusion-restricting glioblastoma, and the potential role of an ischemic microenvironment in facilitating metastatic seeding.

ABBREVIATIONS ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery; GFAP = glial fibrillary acidic protein; H&E = hematoxylin and eosin; TTF-1 = thyroid transcription factor-1.

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We present an unusual case of a 75-year-old man with progressive hemiplegia and hemianesthesia whose initial imaging findings revealed an isolated diffusion-restricting, contrast nonenhancing right basal ganglia lesion with subsequent growth and developing contrast enhancement. Biopsy revealed glioblastoma, *IDH*-wildtype (CNS WHO grade 4), with a concurrent metastasis from pulmonary adenocarcinoma.

Illustrative Case

Clinical History and Presentation

A 75-year-old man initially presenting with back pain was managed by a pain provider with steroid injections and eventually underwent lumbar decompression surgery, after which he noticed left arm and leg weakness that triggered brain MRI. The imaging demonstrated a solitary, well-defined, hyperintense, diffusion-restricting, non–contrast-enhancing lesion in the right basal ganglia most consistent with a subacute ischemic stroke (Fig. 1). The patient was then followed by the stroke neurology team and underwent physical therapy. Approximately 2 months later, the patient presented again with worsening left-sided weakness to near-complete hemiplegia and hemianesthesia. Follow-up brain MRI revealed rapid evolution of the previous solitary right basal ganglia lesion, now with increased signal heterogeneity and persistent peripheral diffusion restriction. Furthermore, there was evidence of a new approximately 3-cm ring-like enhancement in the center of the lesion (Fig. 2). Metastatic workup identified a spiculated lung mass in the right upper lobe, with mediastinal involvement (Fig. 3). Given the patient's neurological decline and interval progression on imaging, a stereotactic needle biopsy of the brain lesion was performed for diagnostic clarification. Histopathological analysis demonstrated metastatic pulmonary adenocarcinoma with concurrent abnormal glial tissue highly suspicious for high-grade glioma (Fig. 4).

Concurrently, the patient underwent a CT-guided biopsy of the right upper lobe lung lesion to inform systemic therapy. While awaiting molecular results, a 2-week course of whole-brain radiation therapy was initiated targeting both intracranial pathologies.

Pathological Analysis

Histopathological evaluation of the stereotactic brain biopsy specimen demonstrated markedly necrotic glial fibrillary acidic protein (GFAP)–positive tissue with neutrophilic and histiocytic inflammatory infiltrates. The viable glial tissue displayed increased cellularity, nuclear pleomorphism with irregular enlarged nuclei, and an atypical myxoid background (Fig. 4A–D). Within the tumor parenchyma, focal areas of coagulative and palisading necrosis were identified, one of the key features of a high-grade glioma (Fig. 5). Although the classic

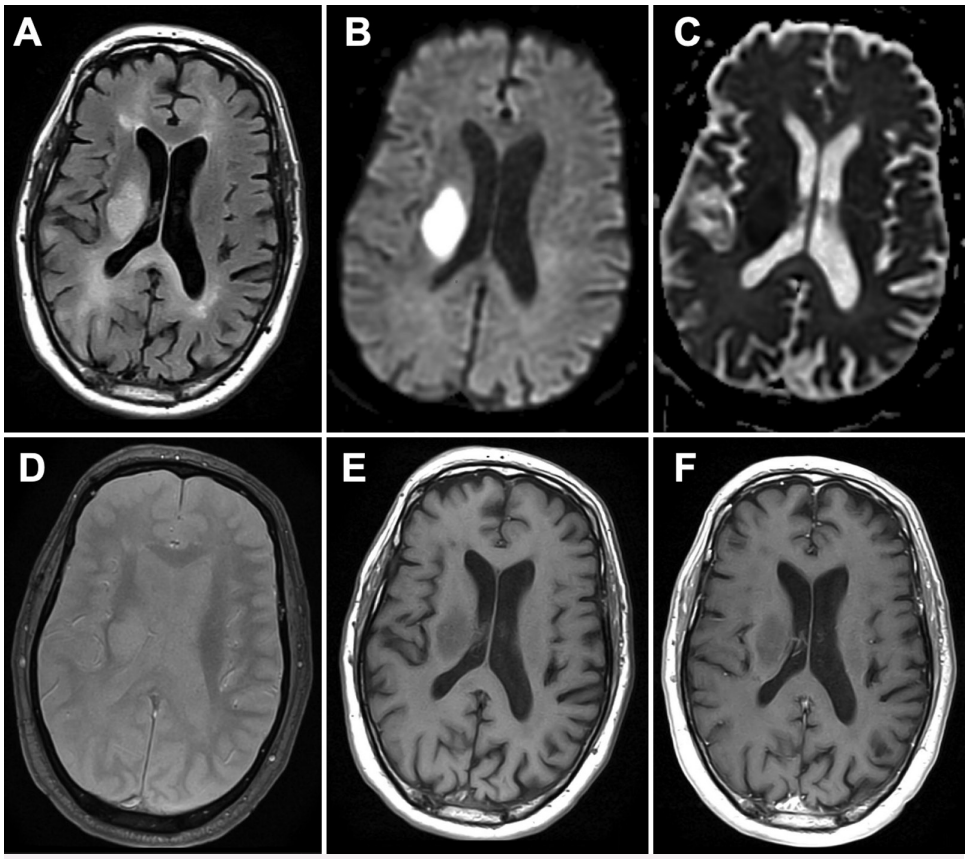

FIG. 1. Initial MR images of the brain demonstrating right basal ganglia ischemic stroke-like changes. T2-FLAIR (**A**), diffusion-weighted (**B**), ADC (**C**), and susceptibility-weighted (**D**) sequences demonstrating a well-defined, hyperintense, diffusion-restricting lesion in the right basal ganglia. The lesion does not demonstrate contrast enhancement, as seen by T1-weighted pre- (**E**) and post-contrast (**F**) sequences, being most consistent with subacute ischemic stroke.

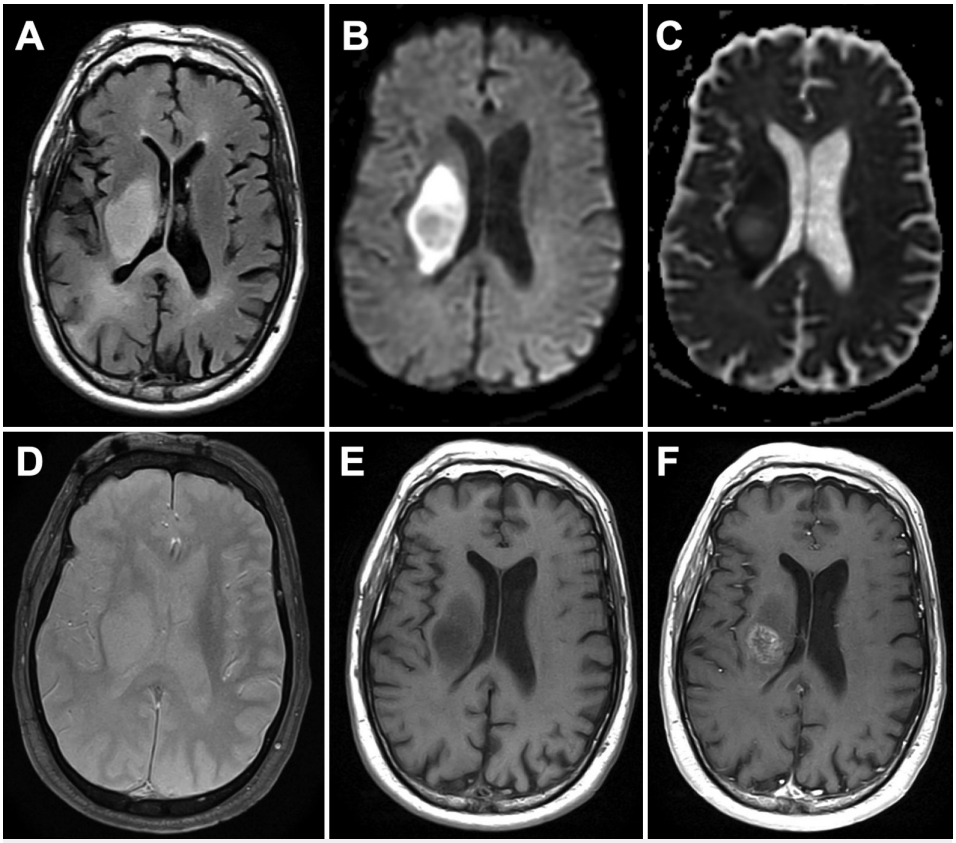

FIG. 2. Two-month follow-up MR images of the brain demonstrating lesion growth and new contrast enhancement. T2-FLAIR (**A**), diffusion-weighted (**B**), ADC (**C**), and susceptibility-weighted (**D**) sequences demonstrating a right basal ganglia lesion, now with increased signal heterogeneity and size as well as persistent peripheral diffusion restriction. There is also new ring-like contrast enhancement in the center of the lesion, as shown by T1 pre- (**E**) and post-contrast (**F**) sequences.

glomeruloid microvascular pattern characteristic of glioblastoma was not observed in this limited stereotactic sample, the presence of atypical vessels and necrosis favor a high-grade neoplastic process. Amid GFAP-positive tissue there were clusters of GFAP-negative epithelioid cells (Fig. 4E) positive for cytokeratin AE1/AE3 (Fig. 4F), CK7, Napsin A (Fig. 4G), and thyroid transcription factor-1 (TTF-1) (Fig. 4H), with weak subset positivity for CK20. Stains for p63 were negative, CD68 highlighted interspersed histiocytes, and p53 demonstrated a wildtype pattern. Fluorescent in situ hybridization analysis demonstrated a chromosome 7 gain (+7) and *CDKN2A/B* hemizygous deletion. There was no detection of a 1p/19q co-deletion, chromosome 10 loss, *EGFR* amplification, *MET* amplification, *MYCN* amplification, *PDGRFRA* amplification, or *PTEN* deletion in the sample. Chromosome 7 gain is frequent in gliomas, but a diagnostic combination of chromosome 7 gain with chromosome 10 loss, seen in *IDH*-wildtype gliomas, was not present in this specimen. NeoTYPE NeoGenomics analysis revealed positive PD-L1 staining in the tumor sample. Molecular testing further revealed the absence of *IDH* and *H3* mutations (*IDH* and *H3*-wildtype), the presence of *NF1* C1682 and W2075 single-nucleotide variants, intact microsatellite instability, low mutation burden, and no detectable RNA fusions. The Ki-67 proliferation index in the glial component of the stereotactic brain biopsy was 5%–10%. Pertinent negative RNA fusions included *BRAF*, *EGFR*, *EGFRvIII*, *NRTRK1/2/3*, *YAP1*, and *ZFTA*. No alterations were detected in *ATRX*, *BRAF*, *EGFR*, *H3-3A*, *HIST1H3C*, *IDH1*, *IDH2*, *MGMT*, or *MYCN* genes. *MGMT* promoter methylation was not detected, while a *TERT* promoter mutation (c.-124C>T) was positive.

Based on the *WHO Classification of Tumours of the Central Nervous System*, 5th edition, this diffuse astrocytic glioma meets diagnostic criteria for glioblastoma by demonstrating an *IDH*- and *H3*-wildtype status with a *TERT* promoter mutation and necrosis.[7] These findings establish the diagnosis of glioblastoma, *IDH*-wildtype (CNS WHO grade 4).

Histopathological examination of the CT-guided right upper lobe lung biopsy revealed neoplastic cells with round to moderately irregular nuclear borders, variably prominent nucleoli, and abundant eosinophilic cytoplasm. Many cells contained intracytoplasmic mucin. The limited size of the tissue fragments and the dyscohesive nature of the cells precluded definitive architectural evaluation. Immunohistochemical staining demonstrated strong, diffuse CK7 positivity; patchy CK20, TTF-1, and villin expression; and positivity for Napsin A. The Ki-67 proliferation index was approximately 10%–20%. When reviewed alongside the patient's recent stereotactic brain biopsy specimen, the lung tumor exhibited identical morphology to the detached clusters of malignant epithelial cells identified intracranially. Next-generation sequencing performed on the lung biopsy specimen revealed a *KRAS* mutation (c.182A>T, p.Q61L, 22%), high tumor mutation burden (13 mutations per megabase), and microsatellite

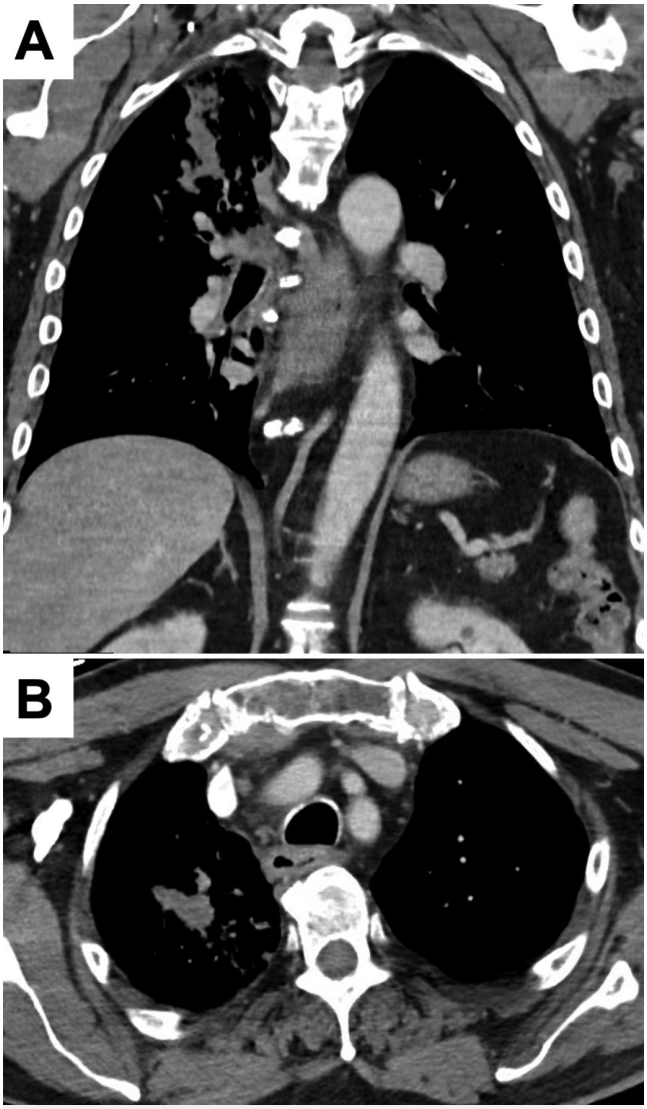

FIG. 3. Contrast-enhanced CT images of the chest showing the lung lesion. Coronal (**A**) and axial (**B**) contrast-enhanced CT images demonstrating a right lung upper lobe mass-like consolidation with irregular borders and internal heterogeneity involving the mediastinum, highly suspicious for primary lung malignancy.

stability. Additional tier 2 alterations included a frameshift mutation in *STK11* (p.E317fs, 25%), a *KEAP1* mutation (p.R272C, 27%), an *ERCC4* frameshift mutation (p.A672fs, 19%), a *STAT3* mutation (p.K290N, 26%), and a *CUL3* splice-site mutation. Unfortunately, there were too few carcinoma cells present in the stereotactic brain biopsy to allow for direct molecular comparison with primary lung adenocarcinoma. These findings supported the diagnosis of pulmonary adenocarcinoma with mucinous features.

As noted above, the patient underwent stereotactic biopsy of the right basal ganglia lesion to obtain diagnostic tissue. While stereotactic biopsy is an established and appropriate diagnostic approach in this clinical context, it inherently limits assessment of spatial anatomical architecture. Consequently, the absence of en bloc resection precludes definitive architectural distinction between a collision tumor and true tumor-to-tumor metastasis based solely on growth pattern. Although en bloc resection would have enabled comprehensive architectural analysis, this approach was not favored given the deep-seated and eloquent location of the lesion and the patient's clinical condition, which together posed an unacceptably high surgical risk.

Importantly, within the constraints of the available tissue, the biopsy demonstrates morphological and immunophenotypic separation between malignant glial tissue and discrete, interspersed clusters of malignant epithelioid cells. The presence of these well-demarcated epithelial tumor nests embedded within a malignant glioma background provides histopathological support for a diagnosis of tumor-to-tumor metastasis rather than a collision tumor

Follow-Up and Outcome

The patient completed a 10-day course of inpatient whole-brain radiation therapy and was discharged in stable condition to a skilled nursing facility with a plan for outpatient medical oncology follow-up. He was ultimately not deemed to be a candidate for further oncological treatment and was transitioned to hospice care 2 weeks after discharge, where he died the following week.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

This case demonstrates a rare intracranial pulmonary adenocarcinoma metastasis into glioblastoma supported by immunohistochemical and molecular studies. Several mechanisms have been proposed to explain the susceptibility of gliomas to metastatic seeding. Glioblastomas exhibit intense neoangiogenesis with a highly permeable blood-brain barrier lacking normal astrocytic end-foot processes.[3] This vascular permeability can potentially facilitate infiltration and secondary growth of circulating carcinoma cells. Additionally, tumor cells within glioblastoma express angiogenic factors such as vascular endothelial growth factor, further promoting a microenvironment conducive to metastatic seeding and growth.[3]

Notably, the patient's initial brain MRI demonstrated a solitary, diffusion-restricting, nonenhancing lesion within the basal ganglia—an imaging profile that is atypical for both high-grade glioma and metastatic disease and is more characteristic of subacute ischemic stroke. Considering the imaging appearance, clinical presentation, and formal stroke neurology evaluation, a diagnosis of subacute ischemic stroke was therefore made at the time. In retrospect, and in the context of subsequent histopathological and molecular findings, this lesion most likely represented a rare glioblastoma subtype with atypical early imaging features, specifically, isolated diffusion restriction in the absence of contrast enhancement, thereby closely mimicking subacute ischemia.

Growing evidence supports the existence of an atypical glioblastoma subtype that initially presents as a nonenhancing, diffusion-restricting lesion prior to the development of classic radiographic features. Ajjikuttira et al. introduced the concept of an "early glioblastoma," which is frequently missed or misdiagnosed due to the absence of hallmark imaging findings.[8] Because of the rapid growth of this tumor, neuroimaging is rarely performed at a sufficiently early stage, and this entity is therefore seldom considered in the initial differential diagnosis.[8] The authors propose that careful evaluation of diffusion-weighted imaging and apparent diffusion coefficient (ADC) maps is critical to improving diagnostic accuracy.[8] Consistent with this

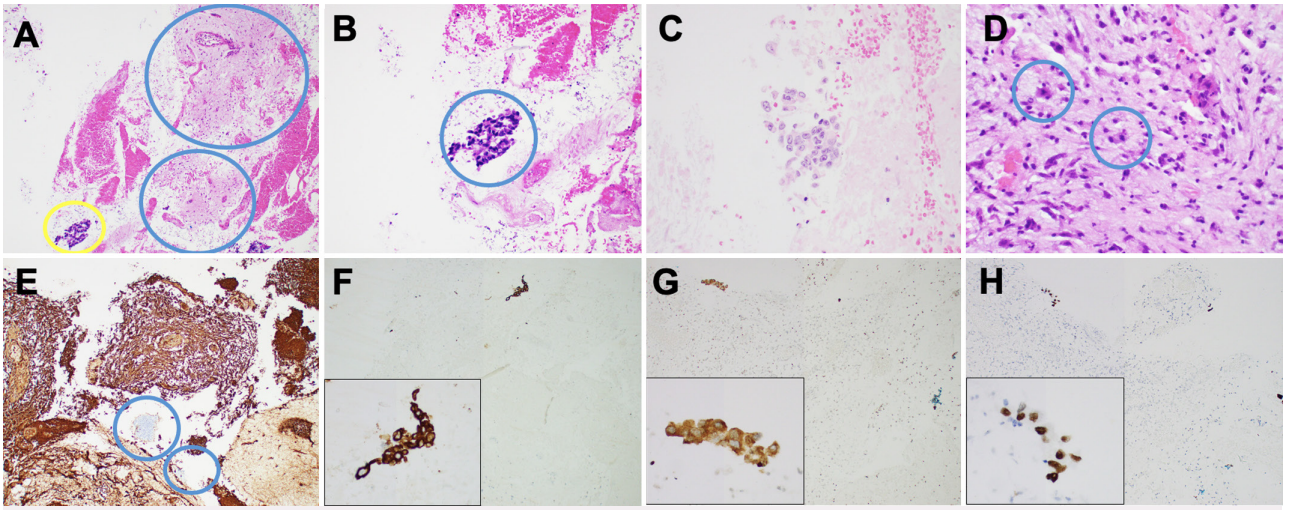

FIG. 4. Histopathological examination of the brain lesion biopsy specimen showing coexistent malignant glial and epithelioid tissue. **A–C:** Hematoxylin and eosin (H&E) staining images at ×100 (A), ×200 (B), and ×400 (C) magnification demonstrating abundant hemorrhage, fragments of malignant glial tissue (*blue circles*), and small clusters of malignant epithelioid tissue (*yellow circle*) of cohesive groups of cells with variable cytoplasmic mucin, irregular nuclear borders, and prominent nucleoli. **D:** Higher-power (×400) examination of the malignant glial tissue revealing atypical nuclei and scattered mitotic figures (*circles*). **E:** GFAP staining highlighting the glial origin of most of the atypical tissue in the submitted material with clusters of nonglial epithelioid cells (*circles*). The two clusters of epithelioid cells are negative for GFAP (*circles*). Background atypical vessels were also identified. **F–H:** Epithelioid cell clusters amid glial tissue were positive for cytokeratin AE1/AE3 (F), Napsin A (G), and TTF-1 (H), supporting a diagnosis of metastatic pulmonary adenocarcinoma (×100 magnification with ×400 enlarged **insets**).

framework, restricted diffusion within the brain parenchyma accompanied by T2–fluid-attenuated inversion recovery (FLAIR) abnormalities, as in this case, is suggestive of early glioblastoma.

This case was further complicated by the lack of contrast enhancement on initial presentation. Although most early glioblastomas have been reported to demonstrate enhancement, several studies have shown that some early lesions may lack this feature.[8,9] Interestingly, in a subset of 27 patients with isolated diffusion restriction without contrast enhancement, 23 developed enhancement within a median of 3 months despite antiangiogenic therapy.[10] This timeline closely mirrors our patient's course, with contrast enhancement emerging within approximately 2 months. Unfortunately, patients with this imaging phenotype appear to experience a more aggressive disease course and shorter overall survival, likely reflecting delayed diagnosis and initiation of definitive treatment.[11]

While the primary interpretation of this case favors early glioblastoma rather than true ischemic stroke, a contributory role of ischemic injury in facilitating metastatic seeding cannot be entirely excluded. Ischemic stroke is known to disrupt blood-brain barrier integrity, promote angiogenic signaling, facilitate rapid tissue remodeling, and induce a pro-inflammatory yet immunosuppressed microenvironment that may be permissive for circulating tumor cell extravasation and survival.[12–16] This hypothesis has recently been tested in a murine model by Prakash and colleagues,[12,17] who demonstrated that prior ischemic stroke promotes the development of brain metastasis. Thus, a preceding ischemic insult could be considered as a permissive factor for metastatic seeding rather than a driver of gliomagenesis in this case.

As previously noted, tumor-to-tumor metastasis involving a glioblastoma has been documented only three times before.[3,5,6] However, 2 of the cases previously reported are now believed to have been a glioblastoma with epithelial differentiation and a collision tumor with metastasis from a sarcomatous component of renal cell carcinoma, respectively.[5,6] The former was originally believed to be tumor-to-tumor metastasis of a glioblastoma with concomitant thyroid carcinoma. However, it was noted that the carcinomatous foci in the glioblastoma had a different profile compared to the primary thyroid cancer.[3,5] The patient had no other metastatic lesions, and immunohistochemical analysis could not trace the origin of the carcinomatous component at that time.[3,5] Therefore, it is now believed that this case was likely a glioblastoma with epithelial differentiation rather than true tumor-to-tumor metastasis.[3] The latter case was originally described as a leptomeningeal metastasis with sarcomatous morphology from a renal cell carcinoma at the edge of a glioblastoma.[3,6] While this case did demonstrate two distinct primary tumors with a recipient and a metastatic donor, both the primary and metastatic lesion had demarcated edges, which is more consistent with a collision tumor than tumor-to-tumor metastasis.[3] Consequently, only a single prior case of tumor-to-tumor metastasis into a glioblastoma has been convincingly documented,[3] underscoring the exceptional rarity of this presentation.

In the case by Fioravanzo and colleagues, the glial components demonstrated GFAP positivity with molecular alterations such as *EGFR* amplification, whereas the epithelial component expressed cytokeratin, TTF-1, and Napsin A, with distinct *KRAS* mutational profiles supporting separate origins.[3] Our case demonstrated a similarly distinct morphological and immunophenotypic separation between the two intracranial neoplasms. However, due to the paucity of intracranial pulmonary adenocarcinoma cells obtained via stereotactic brain biopsy, molecular profiling of the metastatic component could not be performed. As a result, a direct comparison of *KRAS* mutation status between the primary tumors and the metastatic component was not possible.

Lessons

This case underscores the importance of maintaining a high index of suspicion for dual pathology in patients with atypical or

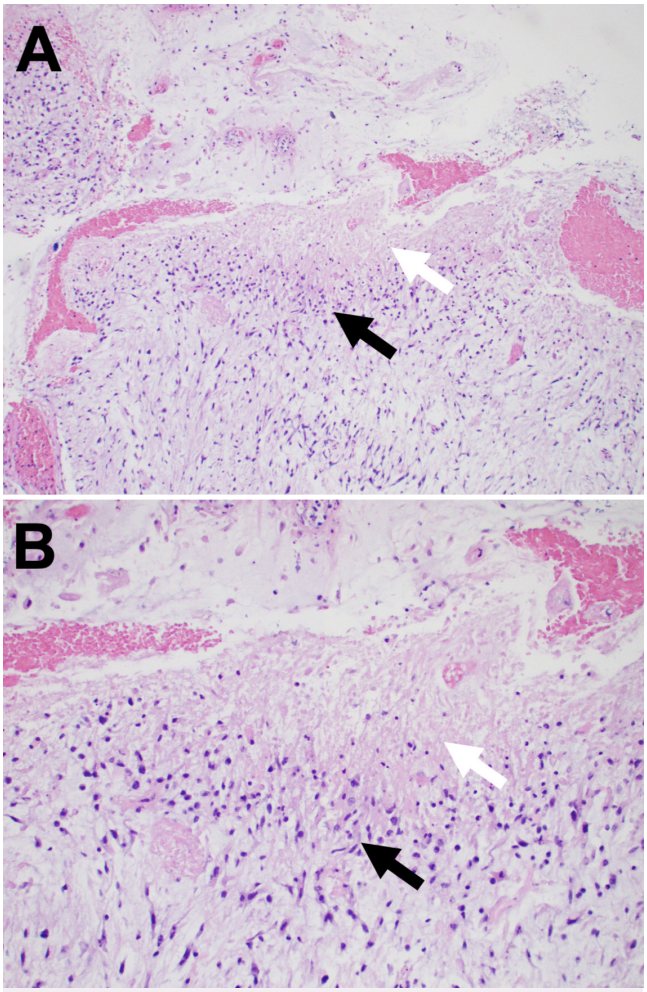

FIG. 5. H&E staining of the brain tumor biopsy specimen highlighting the presence of necrosis. Light microscopy images at ×100 (**A**) and ×200 (**B**) magnification demonstrating areas of nonspecific coagulative (*white arrows* and palisading (*black arrows*) necrosis.

heterogeneous intracranial lesions, particularly when imaging or clinical findings are discordant with a single disease process and progress over time. Additionally, this report highlights the diagnostic value of integrated histopathology, immunohistochemistry, and molecular profiling in identifying composite tumors. This is critical as the recognition of tumor-to-tumor metastasis has significant diagnostic and therapeutic implications and management strategies must consider both the primary CNS tumor and the systemic malignancy. Furthermore, our case contributes to the exceptionally limited body of literature on early glioblastoma presenting with atypical, nonenhancing, diffusion-restricting imaging features. Although ischemic stroke may have theoretically facilitated metastatic seeding, its role in this case remains speculative. While it is not possible to definitively distinguish true tumor-to-tumor seeding from synchronous tumor growth with secondary infiltration, the clear morphological separation and immunophenotypic divergence between malignant cell populations support a diagnosis of tumor-to-tumor metastasis. Early recognition of such cases has the potential to inform prognosis, guide multidisciplinary management, and broaden awareness of this rare and clinically important manifestation of CNS pathology.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ravina, Badra, Cuoco. Acquisition of data: Ravina, Cuoco. Analysis and interpretation of data: Ravina, Badra, Emanuel, Cuoco, Marvin. Drafting the article: Ravina, Badra, Cuoco. Critically revising the article: Ravina, Badra, Cuoco, Marvin, Rogers. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ravina. Administrative/technical/material support: Ravina. Study supervision: Ravina, Rogers.

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