Received: 23 June 2022 | Accepted: 16 November 2022

DOI: 10.1111/bpa.13133

CASE IMAGE

Brain Pathology

A 64-year-old woman with frontal lobe lesion and drug-resistant epilepsy

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Funding information
National Cancer Institute, Grant/Award Number: BC011846-04

1 | CLINICAL HISTORY

A 64-year-old woman with a 29-year history of drug resistant epilepsy presented to the NIH Clinical Center for surgical evaluation. Seizure onset occurred at age 35 with two generalized tonic–clonic seizures. Despite treatment with multiple seizure medications, she continued to experience focal unaware seizures 12–15 times per month. MRI performed at age 58 identified a lesion in the inferior aspect of the left frontal lobe, interpreted as encephalomalacia, with no other known seizure risk factors. Her neurological examination on admission at NIH was remarkable only for mild intentional and postural tremor bilaterally. EEG monitoring was notable for left greater than right frontal interictal and ictal activity. MRI performed at NIH presentation (Figure 1A,B) demonstrated a lesion centered in the left orbitofrontal gyrus unchanged from the MRI performed 7 years prior. The lesion was interpreted as benign, non-neoplastic, most likely representing a hamartoma such as a focal cortical dysplasia, and a likely epileptogenic focus. Intracranial EEG recordings from stereotactically placed depth electrodes in bilateral frontal regions were consistent with seizure onsets in the left frontal lesion region seen on MRI. Surgical resection of the left frontal lobe lesion revealed a firm area with the appearance of scar tissue. The specimen was sent

BOX 1 Virtual glass slide

Access at https://isn-slidearchive.org/?col=ISN&fol=Archive&file=BPA-22-06-162.svs

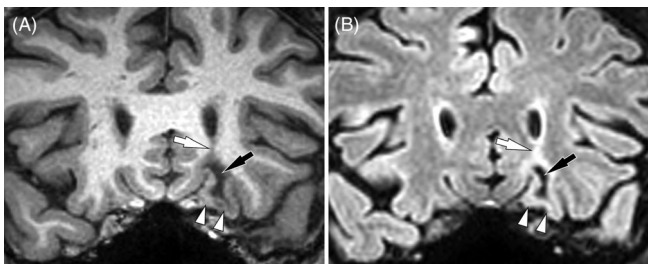

FIGURE 1 Coronal MR images of low signal intensity lesion (black arrow) centered in the white matter of the left medial orbitofrontal gyrus on MPRAGE T1-weighted (A), and T2 FLAIR (B) images. Features include lack of enhancement on T1-weighted MRI (not shown), high T2 signal (not shown). The extension of signal abnormality to the left frontal horn (white arrows) mimics the transmantle sign of cortical dysplasia. The cortical gray matter overlying the lesion is intact (double arrowheads) which would not be expected in post-traumatic or post-infarct encephalomalacia.

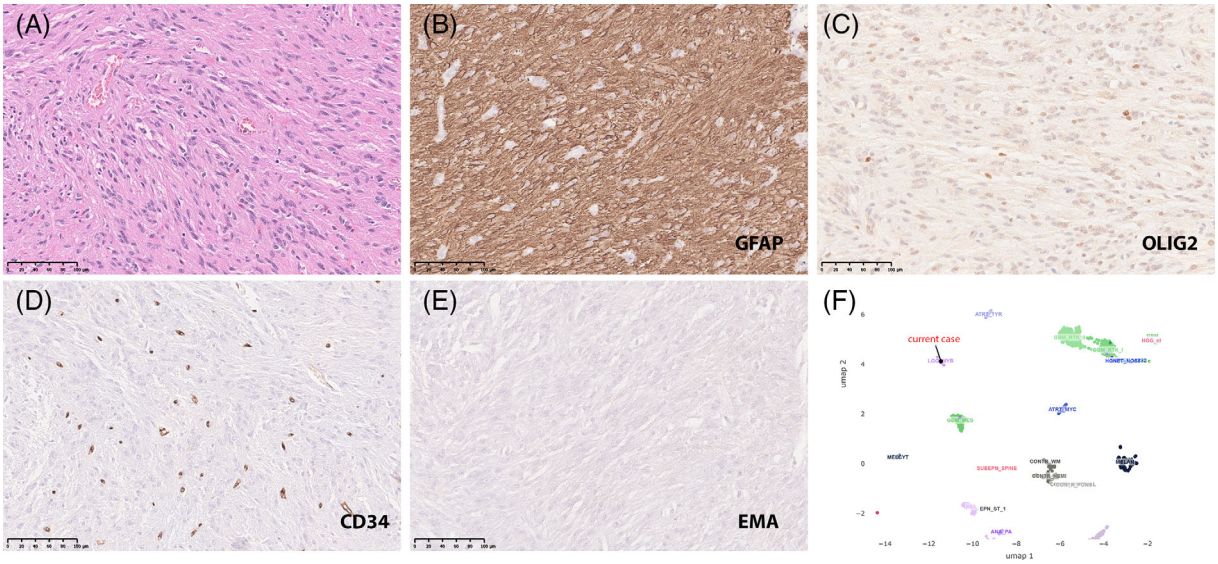

FIGURE 2 Hematoxylin and eosin-stained sections demonstrated the lesion contained monomorphic bipolar spindle-type cells of moderate cellularity (A). Immunohistochemistry studies show the lesional cells are diffusely positive for GFAP (B), predominately negative for OLIG2 (C), negative for CD34 (positive to vessels as internal control) (D), and negative for EMA (E). The immunohistochemistry staining was repeated twice on two different blocks. UMAP clustering analysis of DNA methylation profile data classified this tumor as low-grade glioma (F).

for histologic evaluation. The patient did well postoperatively with no neurologic deficits. She was seizure free for 3 months, although later reported five brief focal seizures occurring over the next 3 months of follow up (Box 1).

2 | FINDINGS

Hematoxylin and eosin-stained sections (Figure 2A) demonstrated a moderately cellular lesion comprised of cytologically bland, spindle-shaped cells without definite perivascular aggregation. Although imaging was negative for neoplasm, we entertained the diagnosis of schwannoma and angiocentric glioma based on H&E review. No necrosis or mitotic figures were evident. Immunohistochemistry studies (Figure 2B–E) revealed the lesional cells were diffusely positive for GFAP and S100, predominately negative for OLIG2, while negative for CD34, EMA, and BRAFV600E. In addition, the lesional cells were negative for IDH1 R132H mutation and retained expression for ATRX. Ki-67 showed low proliferation index (<1%). Collagen IV immunostain was negative. The overall morphological and immunohistochemical profile was more indicative of a low-grade glioma.

DNA methylation microarrays classifier analysis (V11) of this case indicated a match to low-grade glioma, MYB/MYBL1 (calibrated score 0.99). Additionally, the Version 12 classifier further suggested this tumor was a diffuse glioma, MYB(L1)-family, subtype A (calibrated score 0.70) which corresponds to the angiocentric glioma-type. Additional evaluation including Uniform Manifold Approximation and Projection for dimensionality reduction (UMAP) clustering analysis of DNA methylation (Figure 2F) also placed the patient's tumor in the same group. Next Generation Sequencing RNA exome fusion panel analysis showed MYB-QK1 e13:e5 fusion which is known to be associated with angiocentric glioma. The copy number variation plot was essentially flat without detectable chromosomal alterations.

3 | DIAGNOSIS

Diffuse low-grade glioma, MYB/MYBL1 family, most consistent with angiocentric glioma by molecular analysis.

4 | DISCUSSION

Low-grade, developmental, epilepsy-associated brain tumors comprise a major component of tumors in patients undergoing surgery for epilepsy. Characteristic tumors associated with epilepsy include gangliogliomas, dysembryoplastic neuroepithelial tumors, angiocentric gliomas, isomorphic diffuse gliomas, and papillary glioneuronal tumors [1].

The H&E histology of this tumor and immunohistochemistry results were not conclusive as to differential diagnosis of diffuse astrocytoma, MYB-/MYBL1-altered and angiocentric glioma. While the lack of a classical angiocentric pattern and also of EMA immunostaining were not in keeping with a definite diagnosis of angiocentric glioma, DNA methylation analysis, including V12 classifier subtype A (angiocentric glioma type), along with detection of MYB-QKI fusion (rare in diffuse

astrocytoma MYB-altered) was more supportive of a diagnosis of angiocentric glioma [2].

According to the 5th edition of the WHO international classification of human tumors, angiocentric glioma is classified under glioma, glioneuronal tumors and neuronal tumors, and is a subtype of pediatric-type diffuse low-grade glioma. Occasionally, establishing a definite diagnosis for the group of diffuse low-grade gliomas maybe difficult, especially when classic morphology and immunohistochemical features are lacking. Molecular evaluation can be of help in favoring one subtype over the other like in our case.

Angiocentric glioma is a rare and slow-growing low-grade glioma that predominantly occurs in children and young adults with long-standing epilepsy. However, like our patient, cases have been reported in elderly patients. The prognosis of angiocentric gliomas is usually good. In most cases, gross total resection can be achieved and is curative and postoperative complications and tumor recurrence are uncommon [3].

KEYWORDS

angiocentric glioma, DNA methylation, epilepsy, glioma

AUTHOR CONTRIBUTIONS

Xueting Jin wrote the manuscript with input from all authors. John Butman contributed his expertise for the description of the MRI images. Sara Inati, Shareena Rahman, and Kareem Zaghloul contributed their expertise for the description of the clinical and surgical details. Zied Abdullaev, Antonios Papanicolau-Sengos, Drew Pratt, and Kenneth Aldape carried out, interpreted, and provided description of the molecular studies. Martha Quezado helped and supervised the project. All authors reviewed and approved the final manuscript.

ACKNOWLEDGMENTS

We thank the Laboratory of Pathology staff at National Cancer Institution/NIH (Molecular Pathology, Histology, Immunohistochemistry, Surgical Pathology Clinical Sections) who helped prepare and test samples for this case.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. This case report is exempt from sharing of clinical data.

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How to cite this article: Jin X, Abdullaev Z, Butman JA, Inati SK, Rahman SA, Zaghloul KA, et al. A 64-year-old woman with frontal lobe lesion and drug-resistant epilepsy. Brain Pathology. 2023; 33(1):e13133. https://doi.org/10.1111/bpa.13133