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CASE IMAGE

Brain Pathology

Frontal lobe mass in a 46-year-old woman

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1 | CLINICAL HISTORY

A 46-year-old woman presented with new onset seizures. Magnetic resonance imaging (MRI) revealed a 4 cm heterogeneously enhancing mass centered in the right posterior frontal lobe with mild perilesional edema and effacement of the adjacent sulci (Figure 1A). The mass was restricted to cortex and hemispheric white matter, with no involvement of deep grey matter or other midline structures. A retrospective review of MRI studies from 3 years prior demonstrated mild FLAIR signal abnormality in the same location.

The patient underwent craniotomy for resection. Postoperative MRI showed near gross total resection of the mass. The patient declined adjuvant chemotherapy or radiotherapy and was instead treated with intravenous vitamin therapy, hyperbaric oxygen, and additional nutritional supplements. Postoperative imaging at 6 and 12 months demonstrated an enlarging enhancing component at the resection margin (Figure 1B). Re-resection at 12 months following initial surgery confirmed tumor recurrence.

BOX 1 Virtual glass slide

Access at https://isn-slidearchive.org/?col=ISN&fol=Archive&file=BPA-23-07-CI-183HE.svs

2 | FINDINGS

Histologic sections from the initial surgery revealed a moderately cellular glial neoplasm composed of tumor cells with irregular and hyperchromatic nuclei (Box 1,

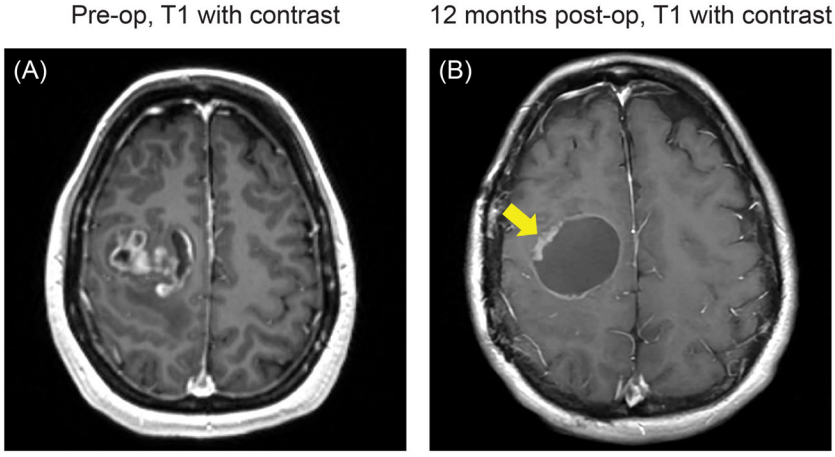

FIGURE 1 Imaging features. Preoperative magnetic resonance imaging (A) demonstrated a heterogeneously enhancing lesion in the right posterior frontal lobe. Postoperative imaging demonstrated near gross total resection, but 6- and 12-month follow-up imaging (B) demonstrated tumor recurrence/progression (arrow).

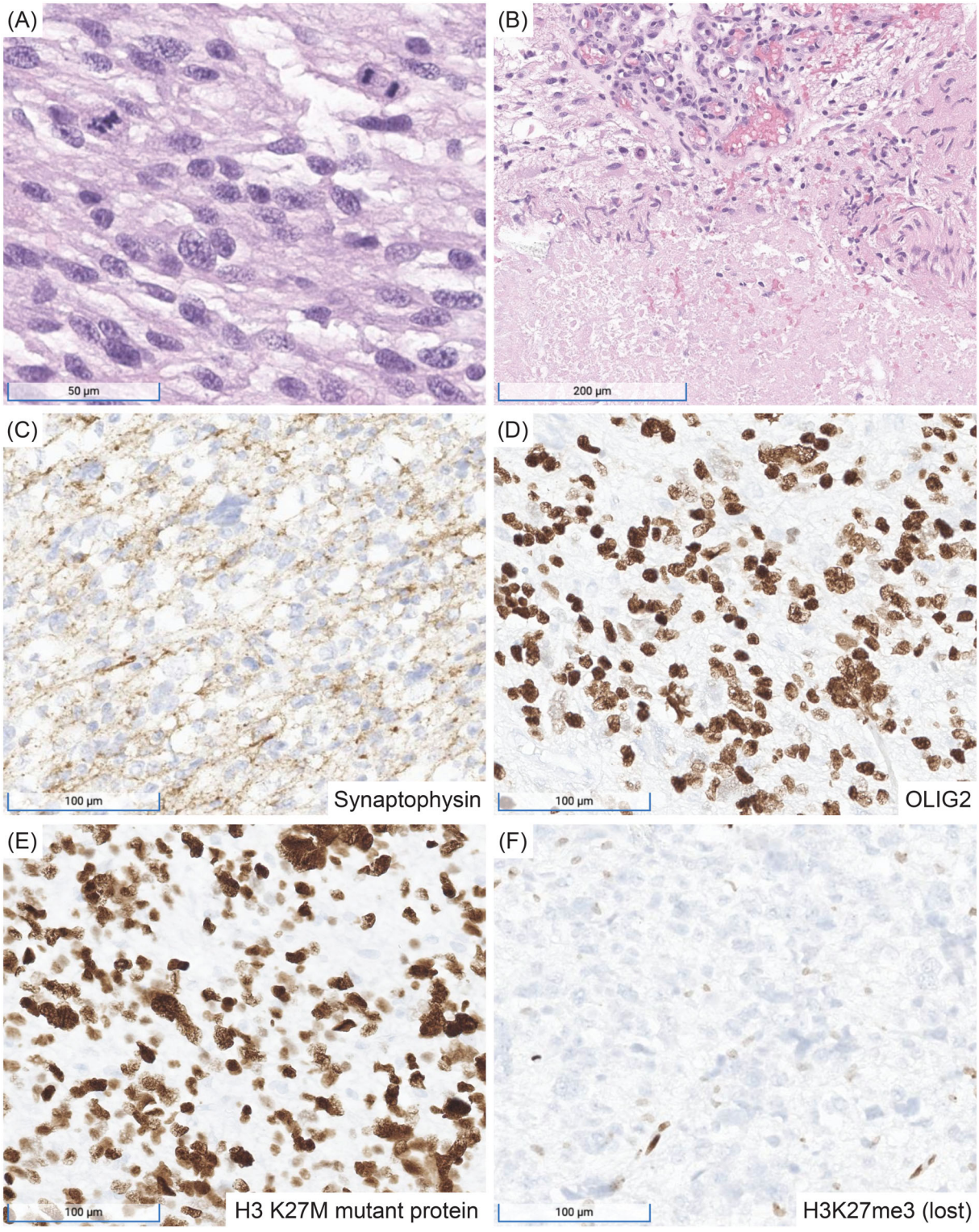

FIGURE 2 Morphologic and immunohistochemical features. Sections reveal an infiltrative glial neoplasm composed of atypical mitotically active cells embedded within a fibrillary background (A). Microvascular proliferation and necrosis were also present (B). Synaptophysin immunostain (C) highlights entrapped axons between tumor cells. The tumor cells are immunoreactive for OLIG2 (D) and H3 K27M-mutant protein (E) immunostains and show loss of expression of H3K27me3 (F).

Figure 2, top row). Foci of microvascular proliferation and necrosis were also seen. The mitotic rate reached up to 6 mitotic figures per 10 high-power fields. Synaptophysin staining highlighted entrapped axons, consistent with an infiltrative growth pattern (Figure 2, middle row). By immunohistochemistry, the neoplastic cells expressed GFAP and OLIG2 but were negative for IDH1 R132H or BRAF V600E mutant protein immunostains. ATRX expression was retained, and p53 labeled only scattered tumor cells.

Next-generation sequencing studies detected *H3F3A* p.K27M (variant allele frequency 42%), *NF1* p.E1192* (85%), and *TP53* p.E171* (9%) mutations. While the tumor harbored gain of chromosome 7, it lacked chromosome 10 loss, *TERT* promoter mutation, or *EGFR* amplification. Retrospective immunohistochemical staining showed diffuse immunoreactivity for H3 K27M mutant protein, along with loss of H3K27me3 expression in tumor cells (Figure 2, bottom row). Methylation profiling performed at NIH/NCI demonstrated a high-confidence match to the "diffuse midline glioma, H3 K27-altered" (DMG) class. Uniform manifold approximation and projection dimensionality reduction analysis also placed the tumor in the "DMG, H3 K27-altered" class.

3 | DIAGNOSIS

"High-grade glioma (HGG), H3 K27M-mutant, not elsewhere classified (NEC)"

4 | DISCUSSION

This case represents a rare example of a diffusely infiltrating HGG centered in the cerebral hemisphere harboring *H3F3A* p.K27M mutation [1] and the first to our knowledge demonstrating an epigenetic signature aligning with "DMG, H3 K27-altered." Midline location is an essential criterion for the diagnosis of DMG according to the 2021 WHO Classification of Tumors of the Central Nervous System. Perplexingly, this case does not involve any midline structures and, therefore, does not meet the contemporary diagnostic criteria for conventional "DMG, H3 K27-altered." As such, the designation of "NEC" was used in this case despite a mutational and epigenetic profile strongly aligning with "DMG, H3 K27-altered." In addition, while this HGG contained areas of necrosis and foci of microvascular proliferation and did not harbor mutations in *IDH1* or *IDH2*, molecular alterations common in "glioblastoma, IDH wild-type" were not identified in this case. The challenge of classifying this tumor highlights inherent challenges following the paradigm shift from histologic classification of central nervous system tumors to an integrated approach based on molecular profiling.

Interestingly, while H3 K27M mutations are widely considered a genetic hallmark of "DMG, H3 K27-altered," hemispheric non-midline histologically low-grade gliomas (LGG) harboring H3 K27M mutation have also been encountered rarely. The H3 K27M-mutant LGG reported to date may appear diffuse or circumscribed, lack microvascular proliferation or necrosis, and have apparent better survival compared to "DMG, H3 K27-altered" [2, 3]. In contrast, the histologic findings in this case (increased mitotic rate, microvascular proliferation, and necrosis) represent features of a HGG. In addition, short-interval follow-up imaging and re-resection in this case demonstrated tumor progression, more consistent with an aggressive natural history as seen in conventional "DMG, H3 K27-altered." The clinical significance of H3 K27M mutation in hemispheric gliomas and the prognostic value of other histologic features (growth pattern, mitotic rate, and necrosis) remains uncertain due to the paucity of cases.

In summary, this case emphasizes the importance of an integrated classification approach for central nervous system tumors, combining clinical presentation, histologic features, and molecular analysis. This case also further emphasizes the need to consider other tumor entities beyond "glioblastoma, IDH wild-type" in the differential of hemispheric IDH wild-type HGG with microvascular proliferation and necrosis. As molecular profiling becomes a foundational aspect of diagnostic neuropathology, the growing challenge of molecular interpretation in unconventional cases underscores the need for periodic revisiting and revising of our contemporary tumor classification system.

KEYWORDS
diffuse midline glioma, H3 K27M, hemispheric

AUTHOR CONTRIBUTIONS
Clinical data collection: KYZ, BR, KCS, CGE. Figure and manuscript text preparation: KYZ, CGL. Study supervision: CGL. All authors made substantial contributions to the conception or design of the study, or to the acquisition, analysis, or interpretation of data. All authors reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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