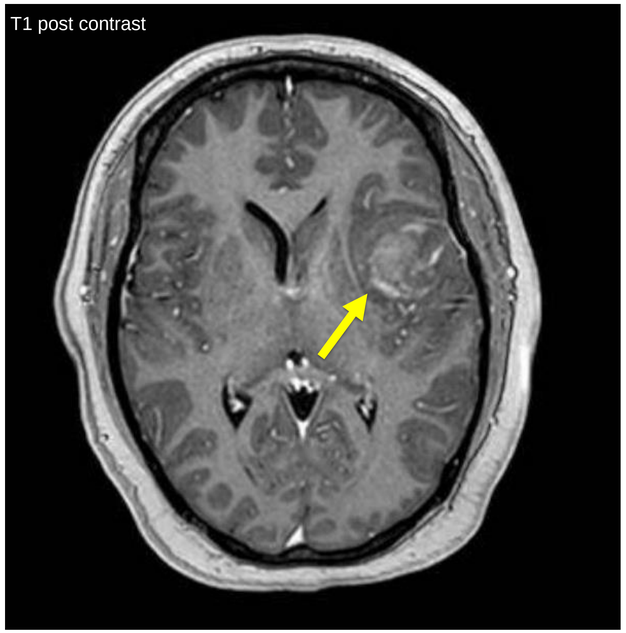
“Pleomorphic xanthoastrocytoma,” “glioblastoma,” or “high-grade glioma, BRAF-altered, NEC”?

Sharika Rajan, MD[1], Khoa Pham, MD[1], Jonathan Dudley, MD, Karisa Schreck, MD, PhD[2], Zied Abdullaev, PhD[3],Martha Quezado, MD[3], Kenneth Aldape, MD[3], Calixto-Hope G Lucas, MD[1]

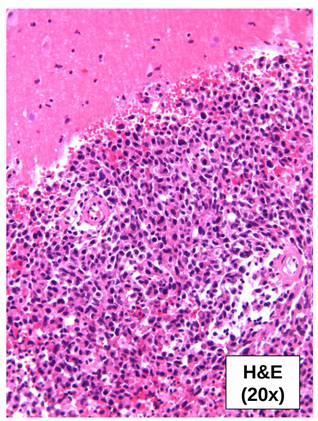
Departments of Pathology[1], and Neurology[2], The Johns Hopkins University School of Medicine, Baltimore, MD, USA
Laboratory of Pathology[3], Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA.

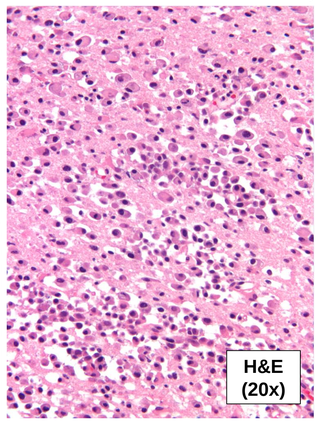
Case Description

- A 34-year-old woman with new onset seizures.
- Magnetic resonance imaging revealed a 4 x 4 cm enhancing mass in the left frontal lobe.

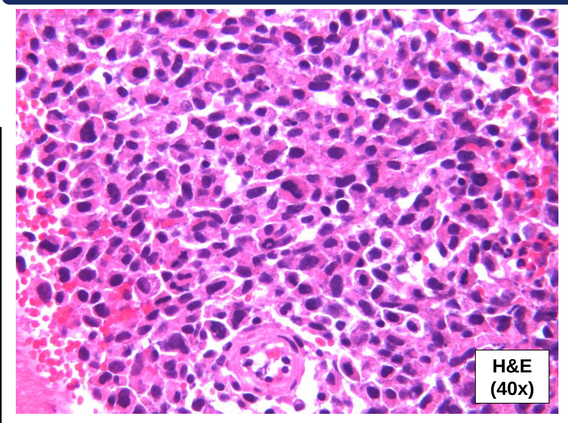


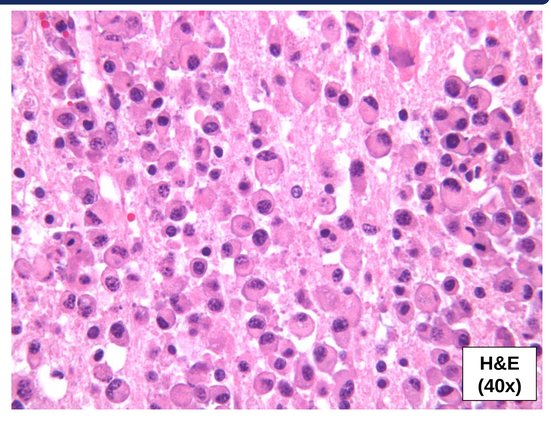
Results

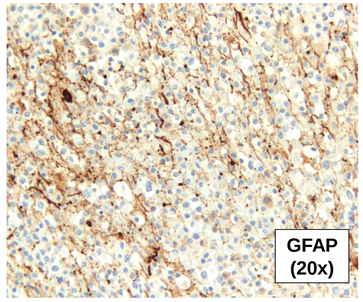


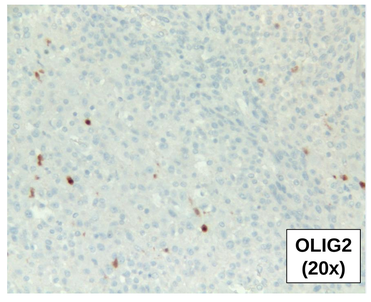


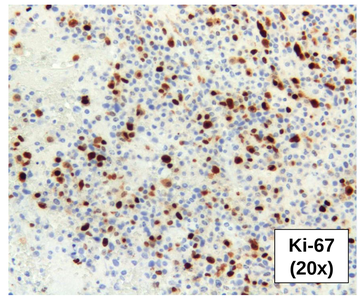
Morphology

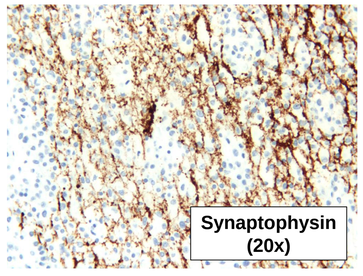


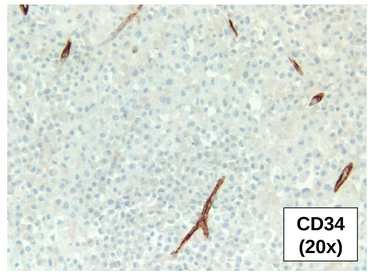


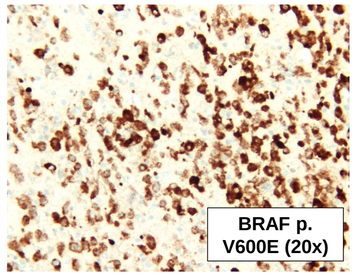








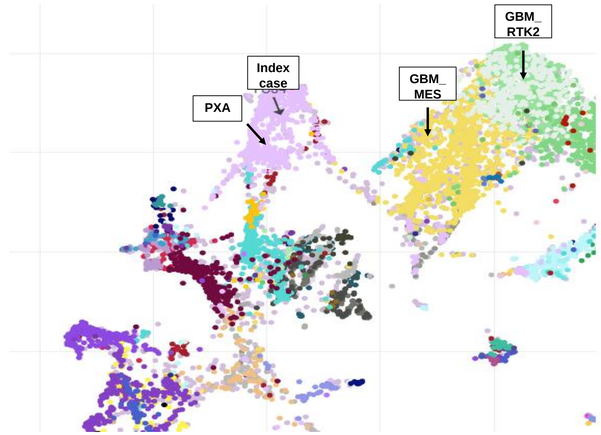




- Mixed solid and infiltrative growth pattern, frequent mitoses, necrosis
- No eosinophilic granular bodies, Rosenthal fibers, multinucleated cells, xanthomatous cells
- Weak focal positivity for OLIG2 and GFAP
- S100 immunoreactive but negative for SOX10, HMB45, Melan A
- Synaptophysin highlights entrapped axons, CD34 highlights blood vessels only
- Tumor cells BRAF p. V600E-positive

Molecular

- Next-generation sequencing confirmed *BRAF* p.V600E and *TERT* c.124C>T mutations and *CDKN2A* homozygous deletion in the absence of *IDH1/2* mutations.
- Methylation profiling did not result in a consensus match to a single methylation class but entertained the possibilities of **pleomorphic xanthoastrocytoma** (PXA - Heidelberg;v11 [score 0.93] and v12 [scoare 0.88]) and **glioblastoma, IDH-wildtype** (GBM - NCI/Bethesda [score 0.98]).
- Uniform Manifold Approximation and Projection dimensionality reduction analysis placed the tumor in the **PXA cluster**.



Discussion

- We report a high-grade glioma with genetic and epigenetic features overlapping between **GBM** and **PXA**.
- The histologic appearance in isolation would be most consistent with GBM, but the possibility of a high-grade PXA cannot entirely be excluded given the patient demographics and ambiguous DNA methylation signature.
- While BRAF-altered GBM and PXA have overlapping genetic alterations (BRAF and TERT activation, CDKN2A inactivation), they typically harbor unique epigenetic signatures. This case is unusual.