# 2018 Diagnostic Slide Session
# Case #8

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Penn Medicine

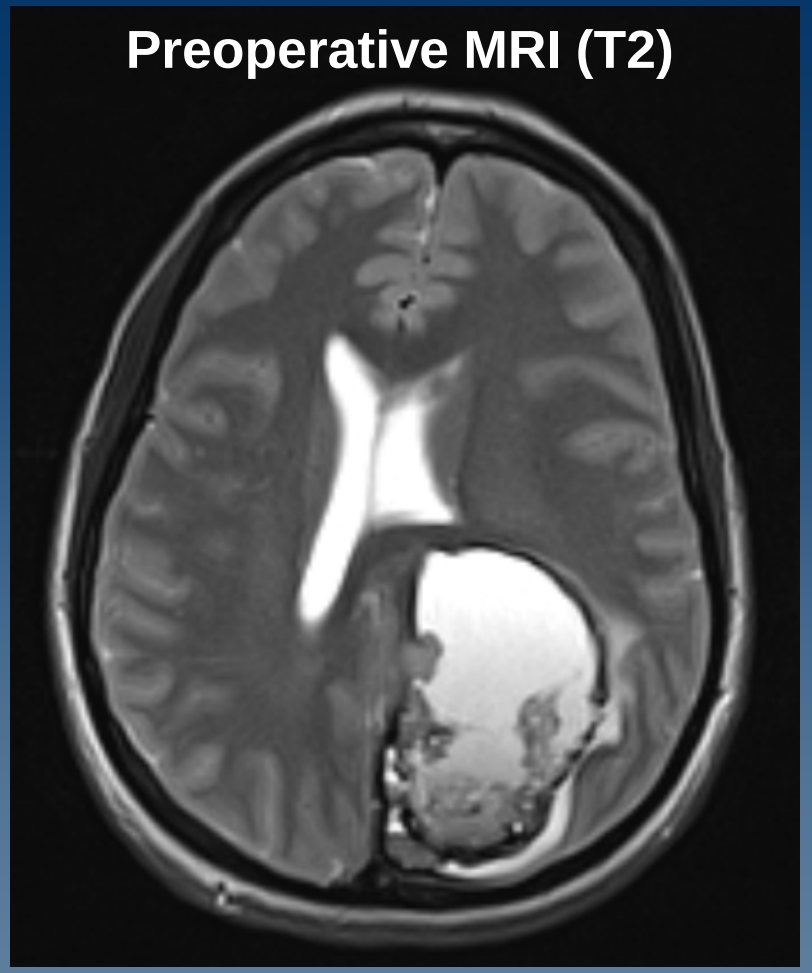
# Disclosures: none

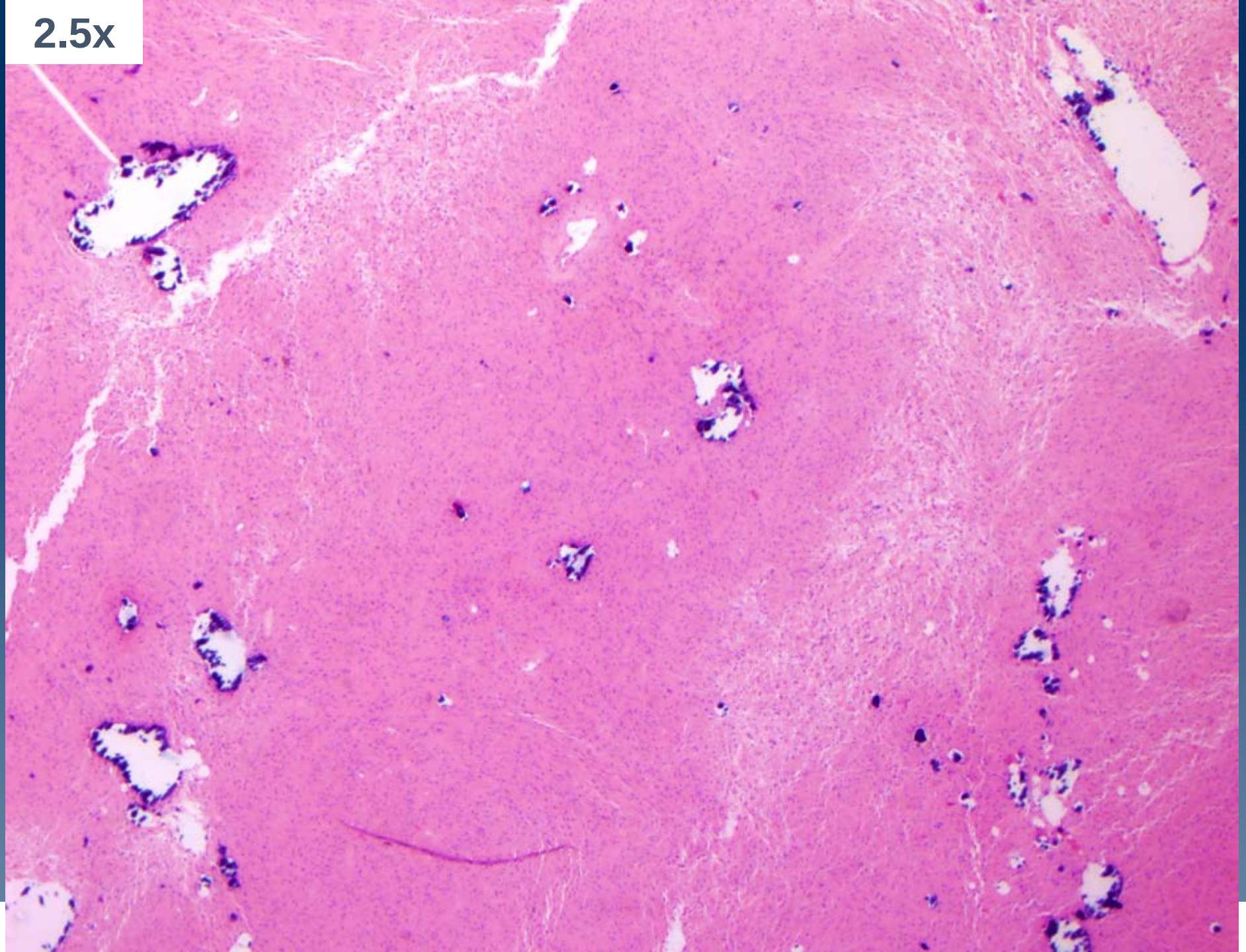
# Clinical History

- Healthy, 38-year-old female presented with headache, nausea and photophobia for 3 days.  She subsequently developed  visual loss and aura in both eyes.
- Past Medical History: None
- Past Surgical History: Ventral hernia repair
- No significant family history or social history

# Imaging

- Large, predominantly cystic left parietal mass measuring 6.4 x 4.3 x 5.2 cm associated with irregular and nodular peripheral enhancement and areas of hemorrhage around its periphery.
- Mass effect including 7-8 mm rightward midline shift and partial effacement of the basal cisterns.

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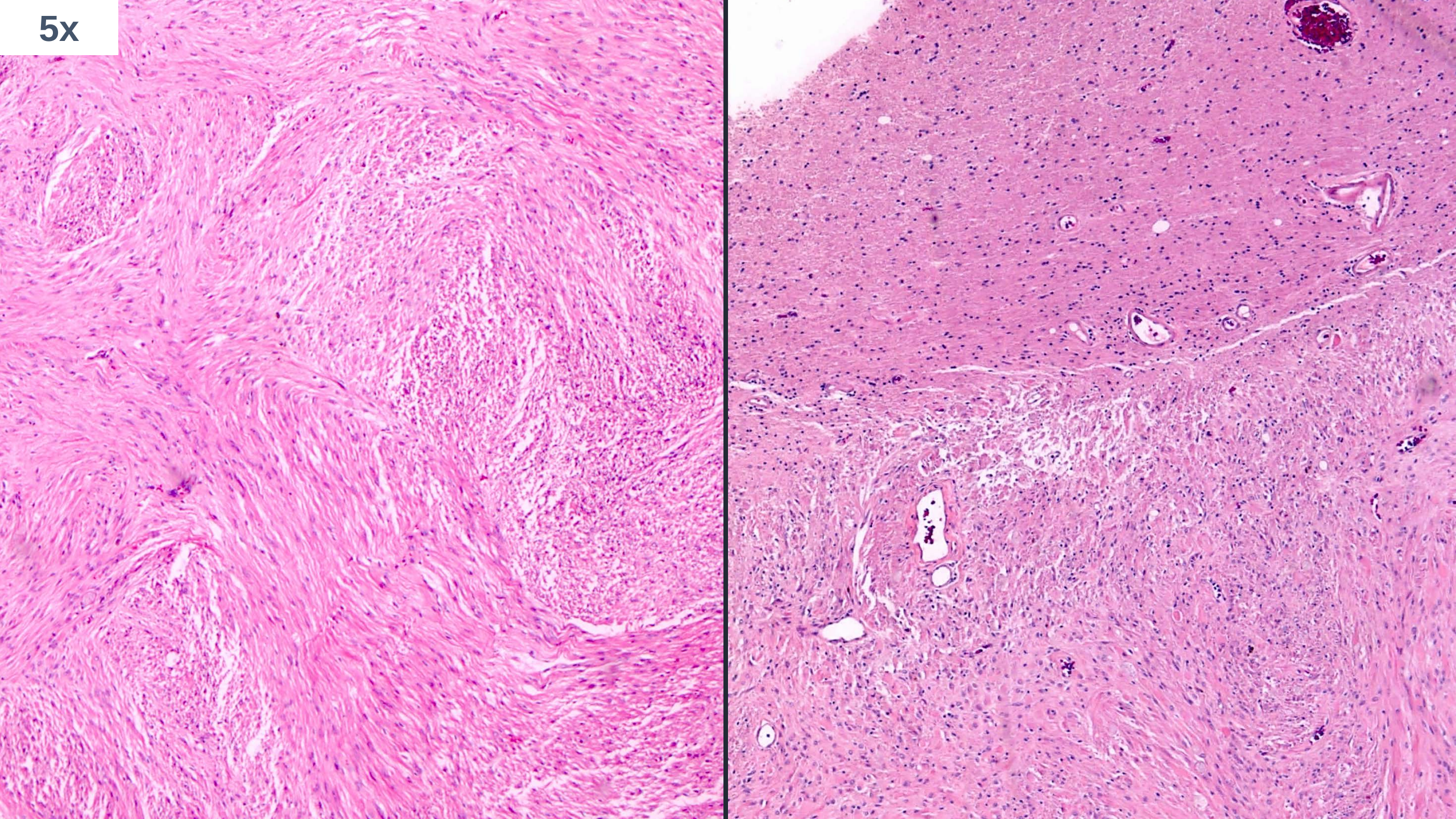
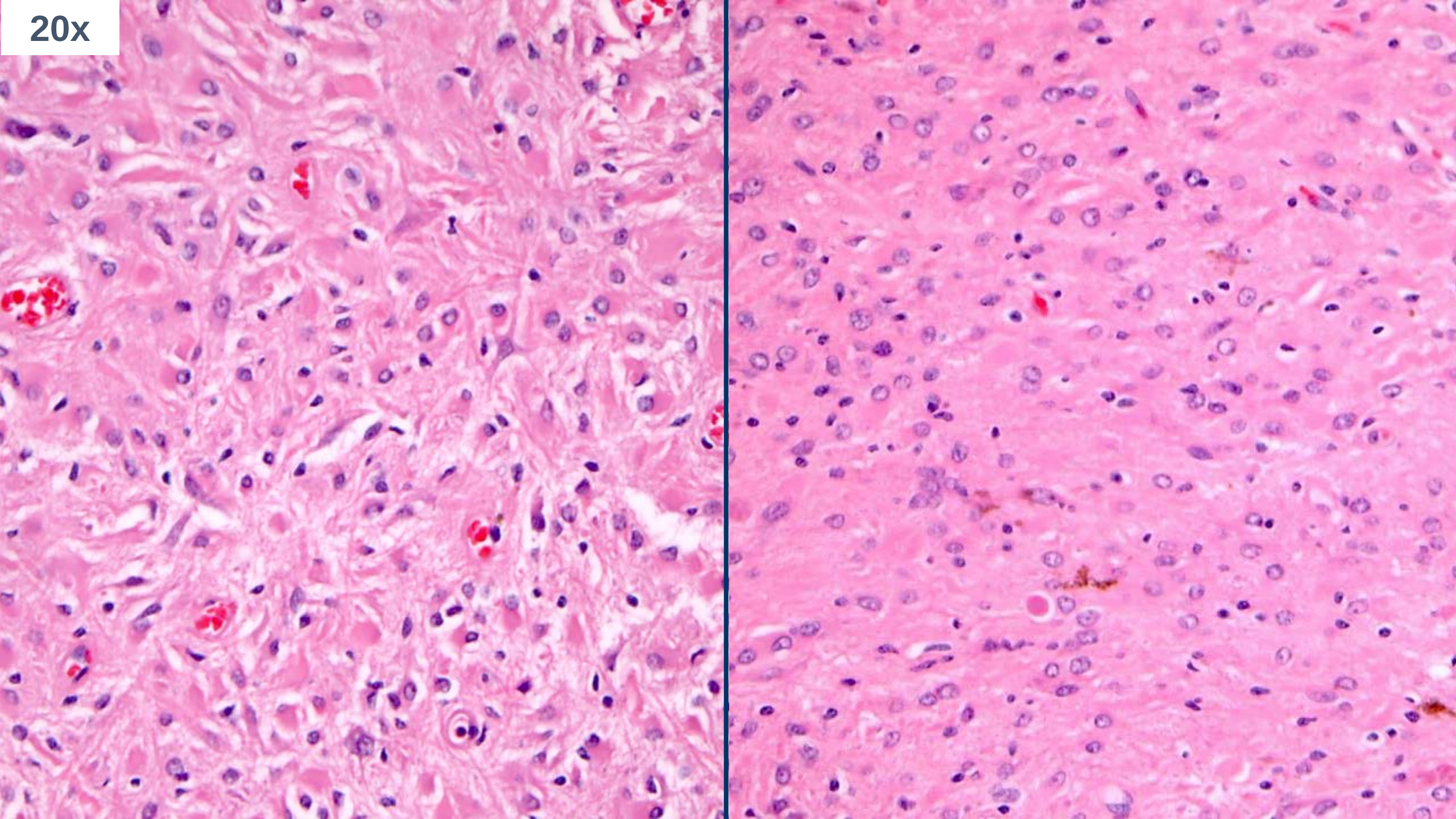

5x


20x

# Differential Diagnosis?

# Our Differential

- Pleomorphic xanthoastrocytoma
- Meningioma
- Pilocytic astrocytoma
- Ependymoma
- Subependymal giant cell tumor
- Melanocytic tumor
- Diffuse astrocytoma (lacking infiltration)
- Histiocytic lesion
- Nerve sheath tumor
- Metastasis

# Immunohistochemistry

- **Positive stains:**
  - GFAP
  - S100: cytoplasmic
  - EMA: weak, patchy staining
    - No perinuclear dots or rings
  - Ki-67 < 1%

- **Negative stains:**
  - IDH1-R132H
  - SSTR2A
  - Neurofilaments
  - Synaptophysin
  - Keratins
  - SOX10
  - HMB45
  - MITF2
  - STAT6
  - CD68 and CD163
  - p53 (wildtype)

# Integrated Diagnosis

- **Brain, left parietal tumor, resection:**
  - **Integrated diagnosis: Pending**
  - **Histologic diagnosis: Low grade glioma**
  - **Histologic grade: Low grade (I-II)**
  - **Molecular information: IDH1-R132H negative (by immunohistochemistry), pending additional molecular/genetic studies**

# Molecular Findings

- Next generation sequencing on a panel of 152 genes (which includes among others: *BRAF, p53, ATRX, EGFR, TSC1, TSC2, IDH1* and *IDH2* genes) showed a normal sequencing study

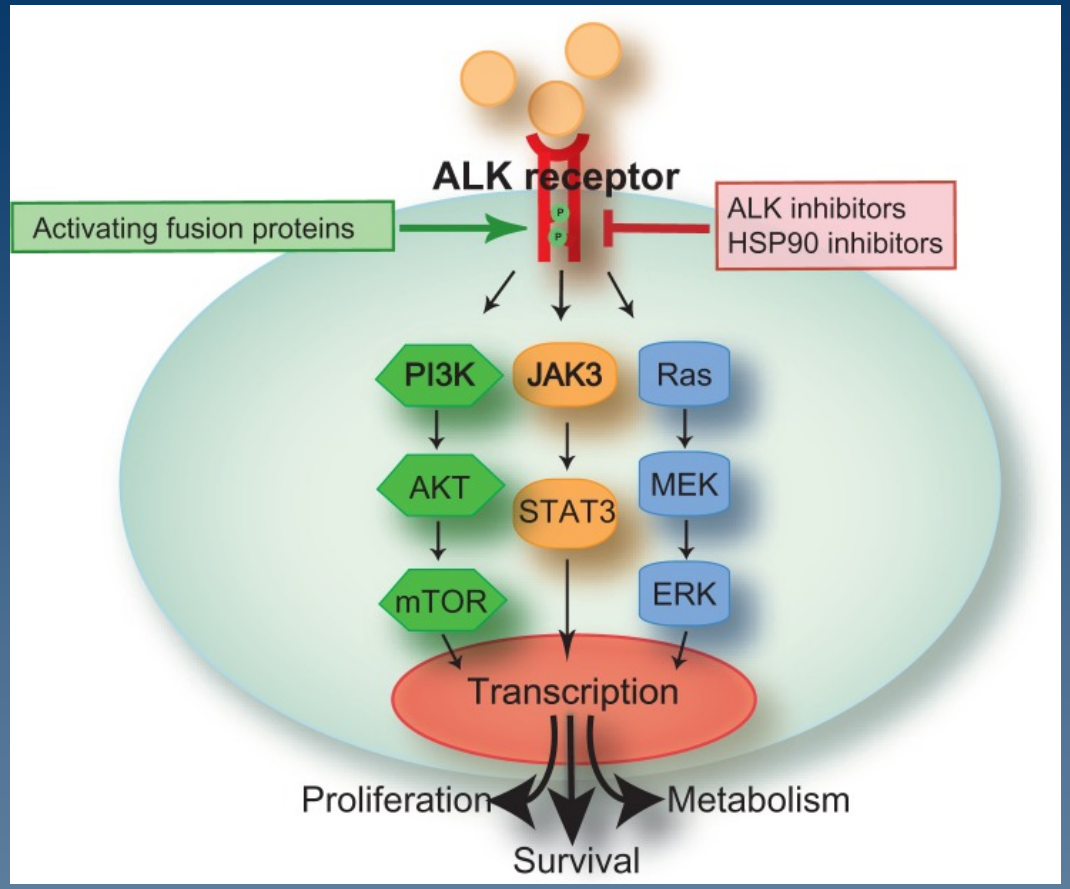
- A Cancer Gene Fusion panel showed a *FXR1* (NM_005087.3)-*ALK* (NM_004304.4) fusion
  - A *BRAF* fusion was not identified

# Final Integrated Diagnosis

- **Brain, left parietal tumor, resection:**
  - **Integrated diagnosis: Low grade glioma, IDH-wildtype, *FXR1-ALK* fusion**
  - **Histologic diagnosis: Low grade glioma**
  - **Histologic grade: Low grade**
  - **Molecular information: *FXR1-ALK* fusion, IDH-wildtype**

# ALK Rearrangements

- *ALK* (Anaplastic Lymphoma Kinase) encodes a receptor tyrosine kinase
- ALK fusions are seen in anaplastic large-cell lymphoma, inflammatory myofibroblastic tumors, thyroid carcinomas, and non–small cell lung cancers
- The ALK fusion protein results in constitutive activation of signaling pathways that increase cell proliferation of survival, leading to cancer formation
  - Exons 20–29 encode the tyrosine kinase domain of ALK
  - Most partners contain coiled-coil or leucine-zipper domains
    - Drive the oligomerization necessary for ligand-independent activation

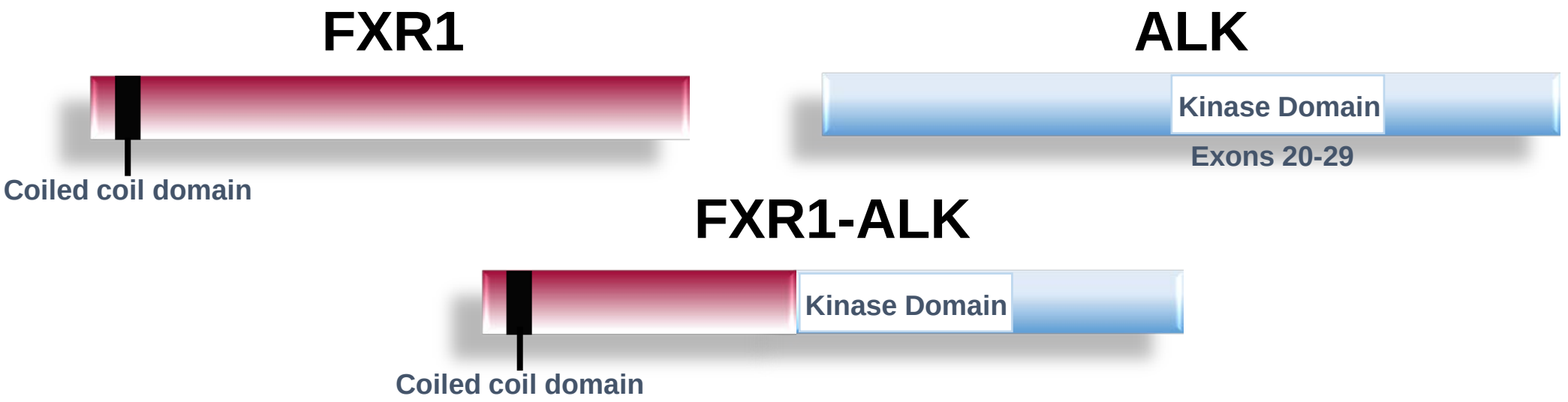




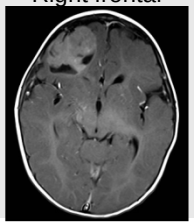
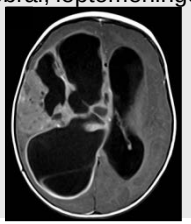
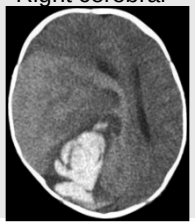
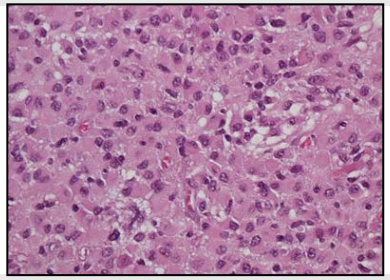
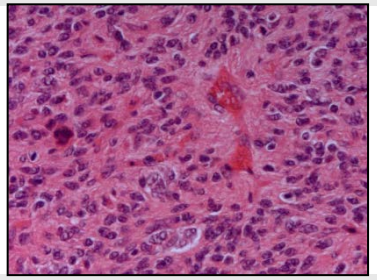
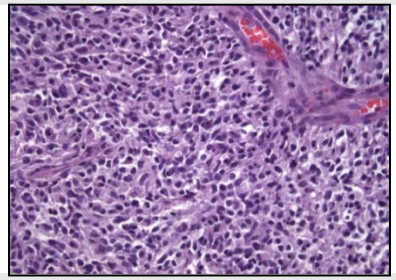

Roberts PJ. *Biologics*. 2013

# Our Tumor

## *FXR1* exon 13 - *ALK* exon 20



# Gliomas with ALK Rearrangements

| | Olsen et al. 2015 #1 | Olsen et al. 2015 #2 | Aghajan et al. 2016 |
|---|---|---|---|
| Age | 8 months | 9 months | 3 months |
| Gender | M | F | F |
| Tumor Location and MRI | Right frontal  | Right cerebral, leptomeningeal spread  | Right cerebral  |
| Histologic Diagnosis | Intermediate-grade glioma with features suggestive of ependymoma | Anaplastic ependymoma/ glioblastoma | Malignant glial tumor |
| Histologic Grade | II-III | III-IV | High Grade |
| Histology |  |  |  |
| Fusion | *KTN1-ALK* | *CCDC88A-ALK* | *PPP1CB-ALK* |
| Treatment | Gross total resection, no chemotherapy/radiation | Resection and chemotherapy | Gross total resection, no chemotherapy/radiation |
| Follow-up | No sign of recurrence at 6.5 years | No disease progression 22 months after discontinuation of chemotherapy | Disease-free at 3 years with motor and neurocognitive delays |

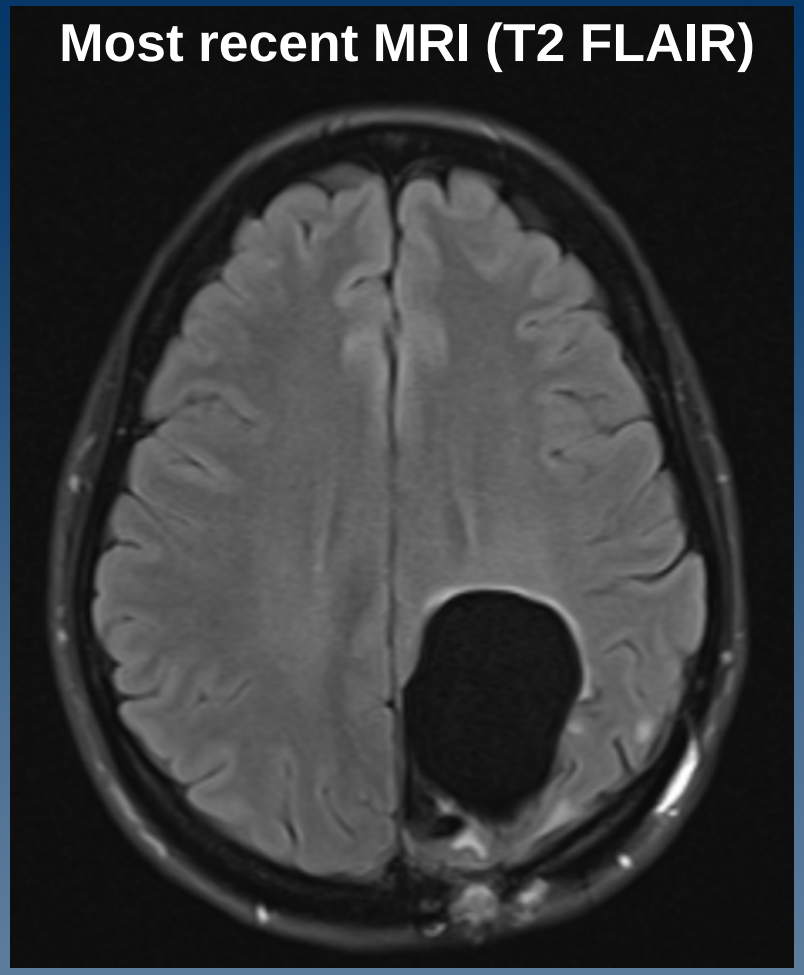
**Histology often difficult to classify, has been proposed to potentially represent a new tumor entity**

# Therapeutic Implications

- Therapies for *ALK* gene alterations are predominantly associated with *ALK* gene fusions
- Crizotinib: selective adenosine triphosphate–competitive small-molecule oral inhibitor of ALK, c-MET, and ROS1 receptor tyrosine kinases and their oncogenic variants
  - Phase III studies showed crizotinib was superior to standard first-line chemotherapy in patients with previously untreated advanced *ALK*-rearranged NSCLC
  - FDA approved (2011) for metastatic NSCLC whose tumors are positive for *ALK* fusions
  - Crizotinib also effective in treating IMT and pediatric ALCL
  - Durable responses uncommon due to the development of resistance, leading to disease progression
  - Plasma concentration significantly higher than CSF suggesting poor blood-brain barrier penetration
- Most crizotinib-resistant tumors are sensitive to more potent, structurally distinct, second-generation ALK inhibitors
  - Ceritinib and alectinib are FDA approved for treatment of NSCLC
  - Initial studies have shown promising response in NSCLC CNS metastases

# Patient Follow-up

- Gross total resection and no chemotherapy/radiation
- 1.5 years after surgery: Doing well, KPS-80, unable to drive because of right visual field cut which has been slowly improving
- MRI: Left parietal craniotomy for tumor resection without evidence of neoplastic progression. Stable foci of susceptibility and curvilinear enhancement about the resection cavity.



# Take Home Points

- Common characteristics of CNS tumors with *ALK* fusions:
  - Pediatric and young adult patients (3 months - 38 years)
  - Located in the cerebral hemispheres, well circumscribed, cystic
  - Gliomas with unique histology; may be low or high grade
  - All patients with no evidence of recurrence (follow-up: 1.5-6.5 years)
- ALK inhibitors (especially second-generation) are effective in treating tumors with *ALK* fusions, show promising CNS penetration and have a tolerable side-effect profile
- The precise role of *ALK* fusions in glioma tumorigenesis and the clinical and therapeutic significance remain to be defined

# References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