Case 2022-1

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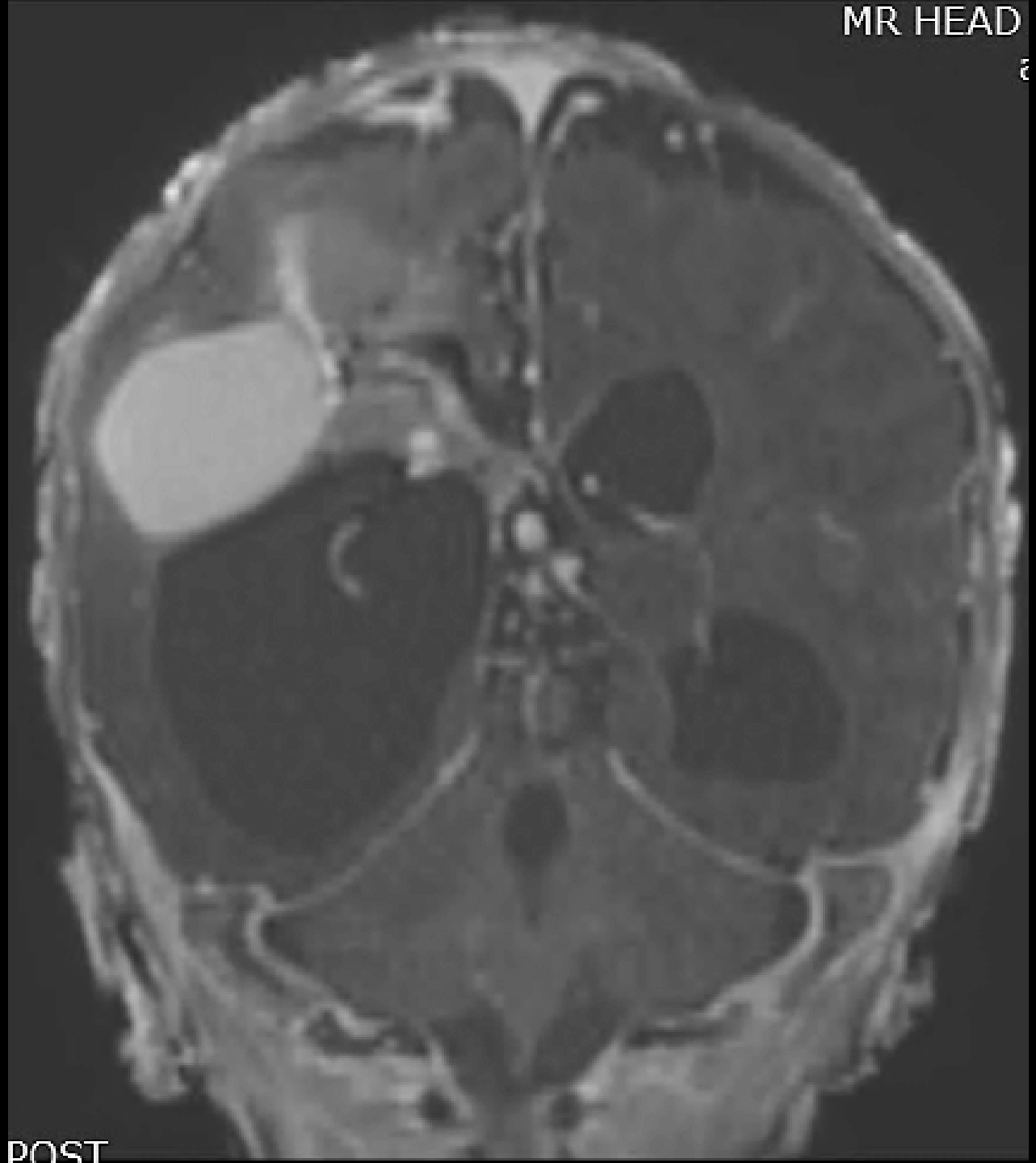
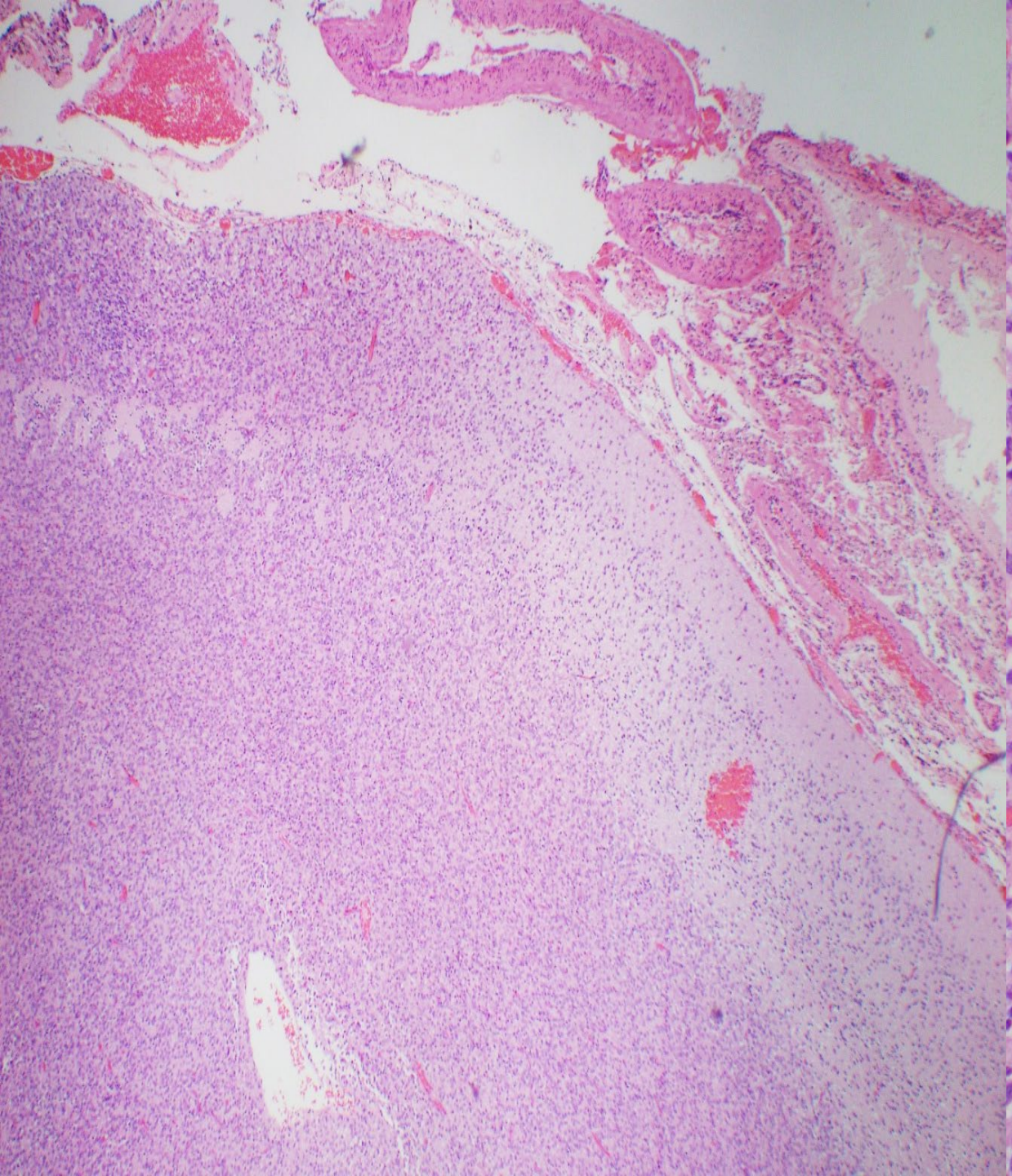
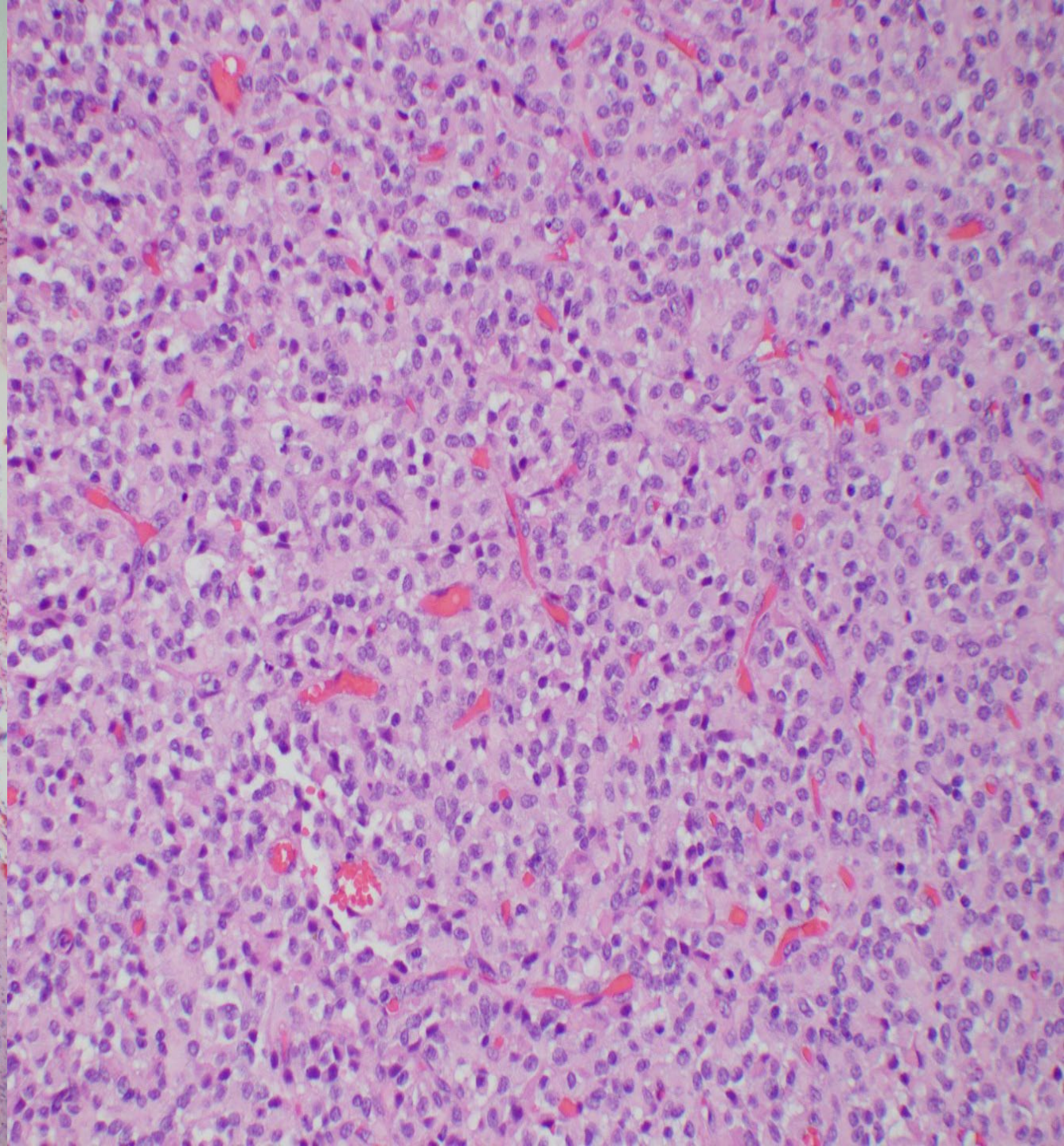
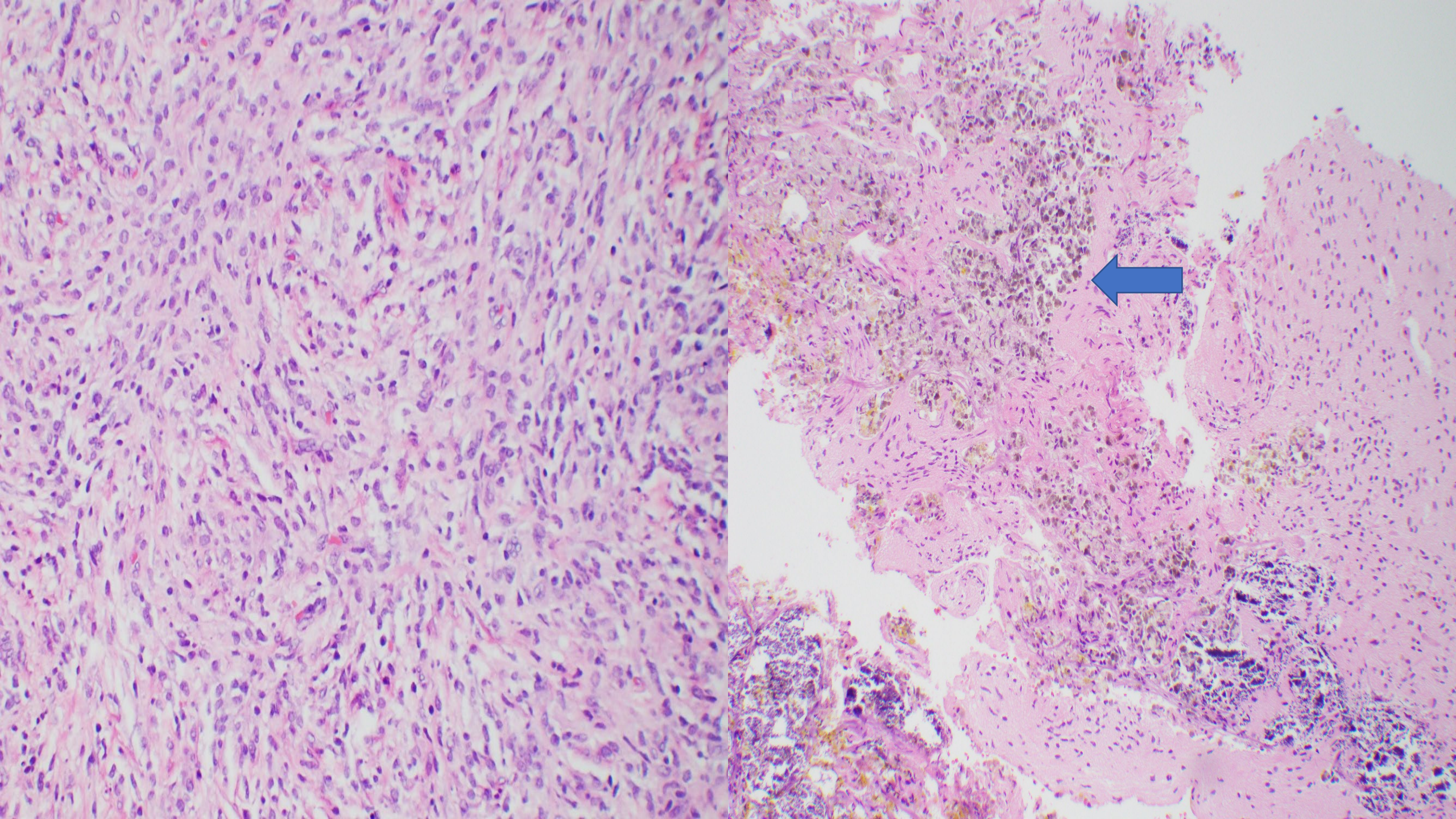
Clinical History

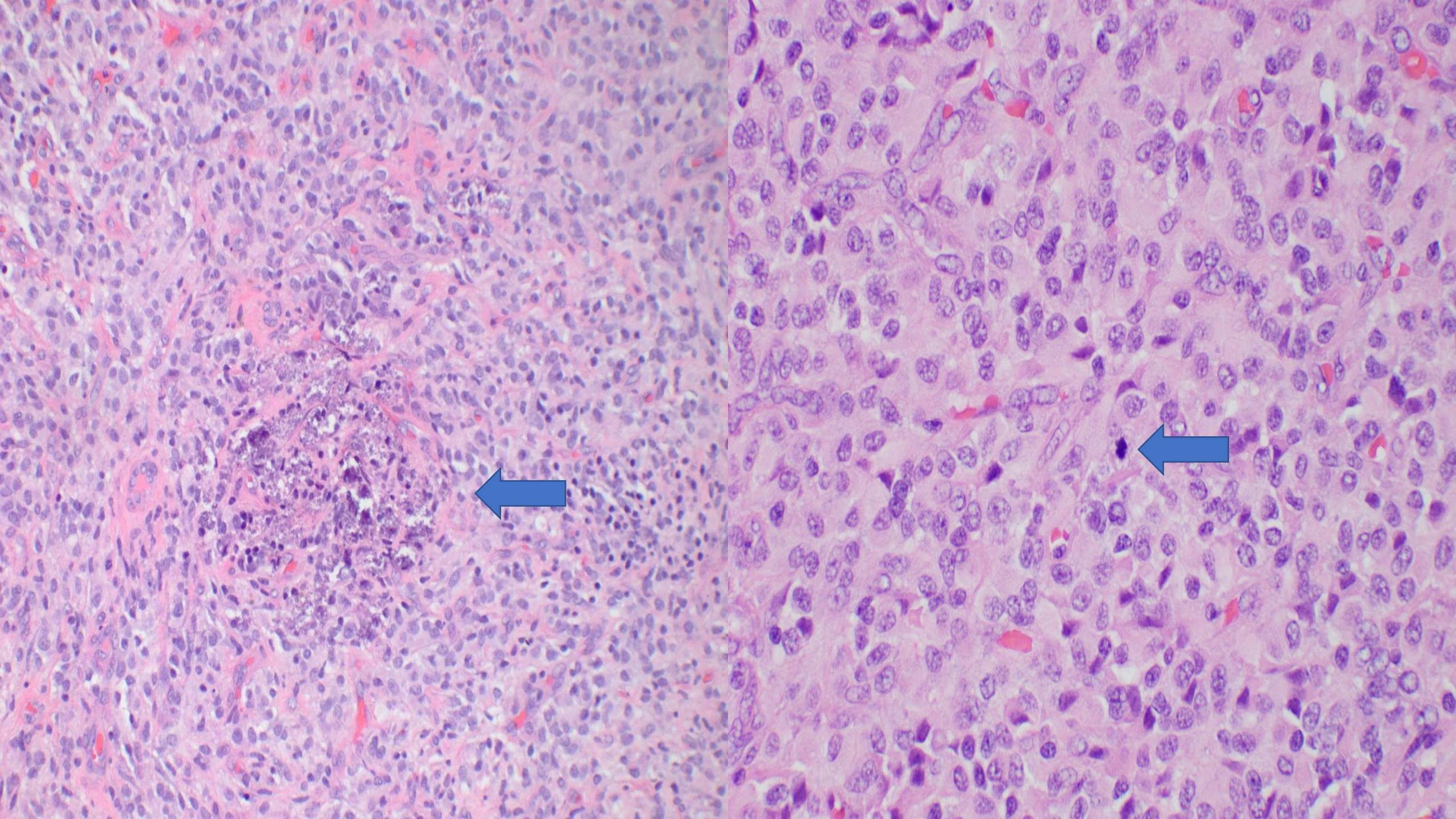
- Thirteen-day-old female who presented with respiratory distress and apnea found to have an AV fistula and ventriculomegaly due to a mixed solid and cystic hemorrhagic mass located within the right frontal and parietal lobes shown in the following image.

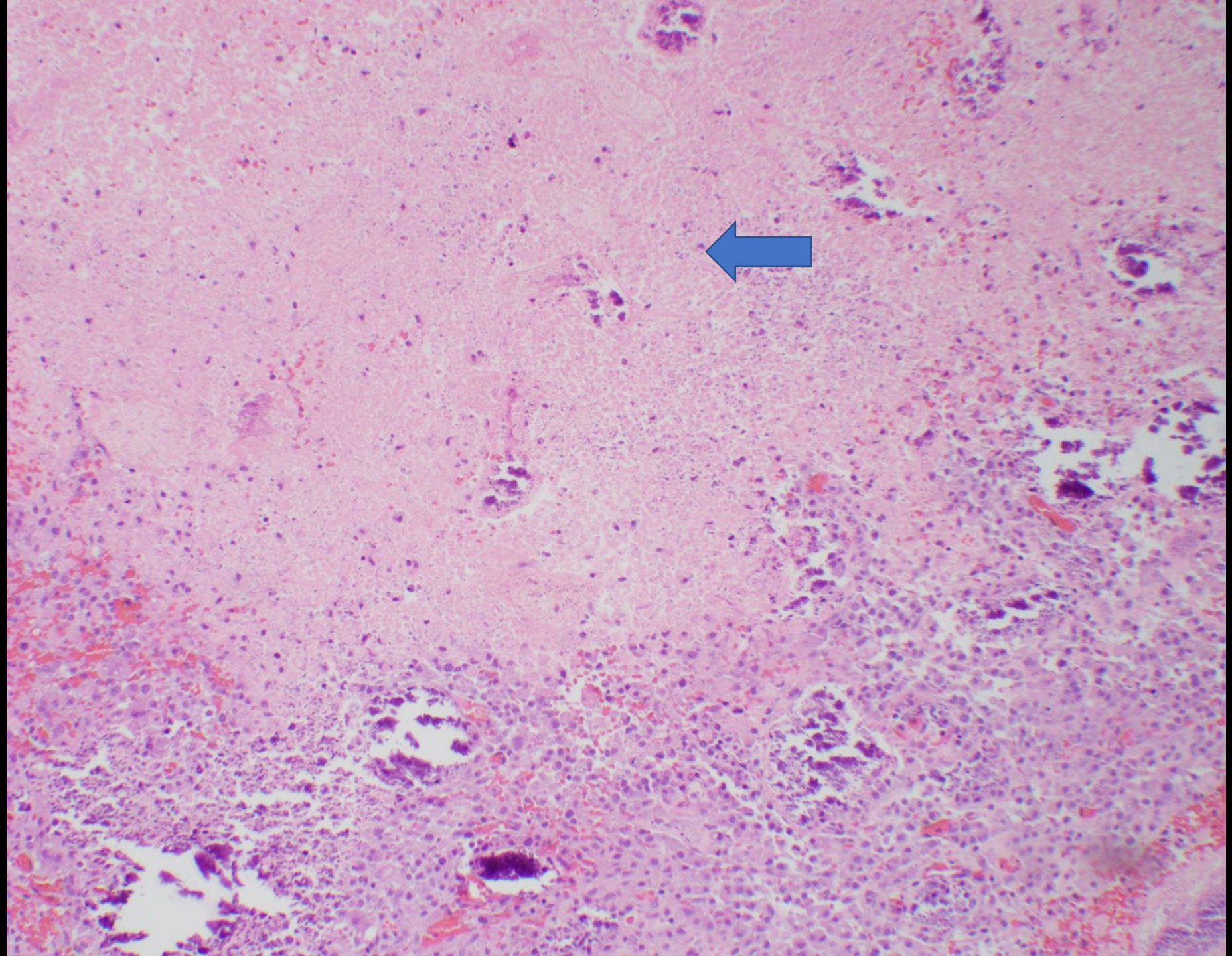
MRI



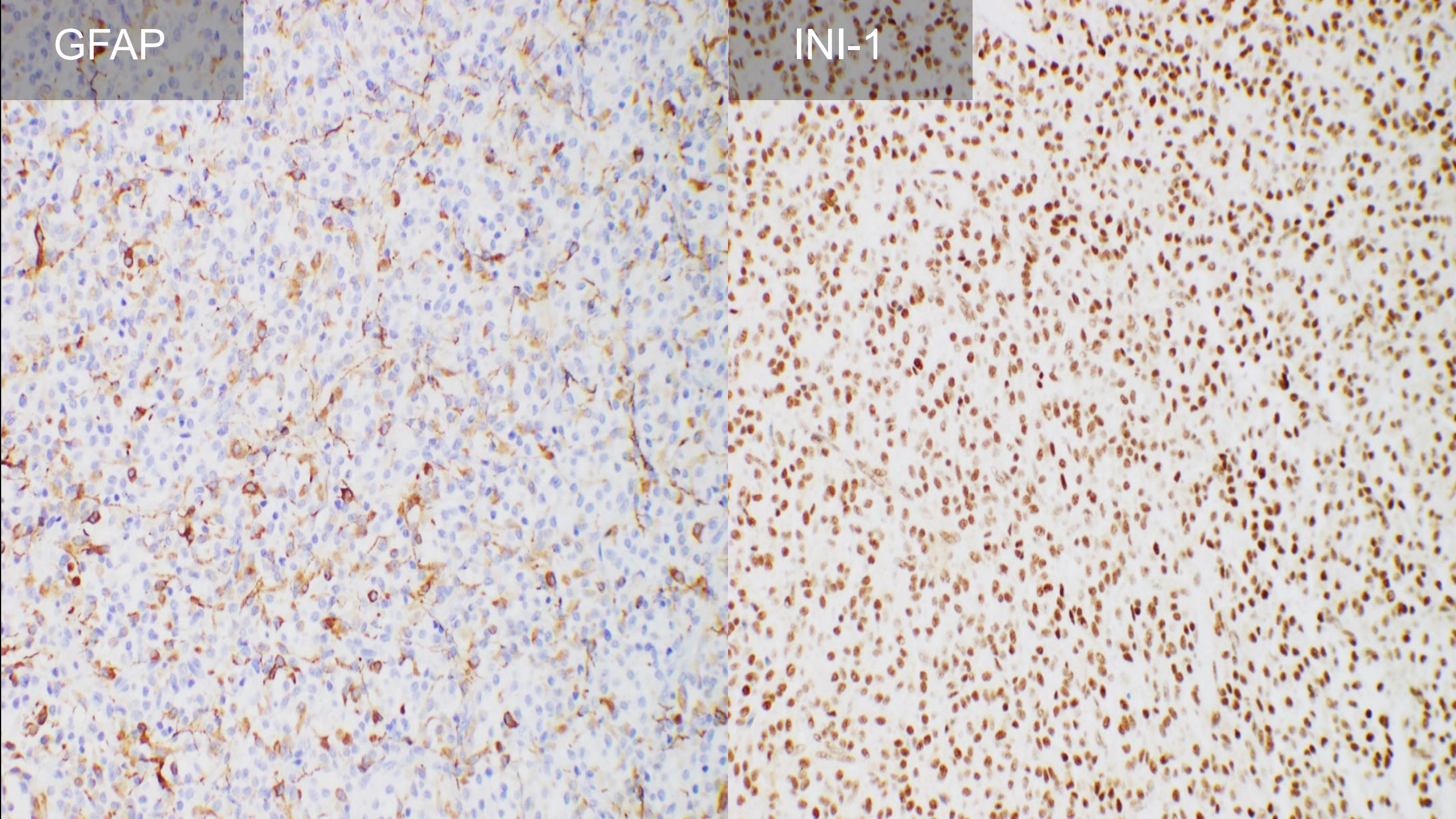



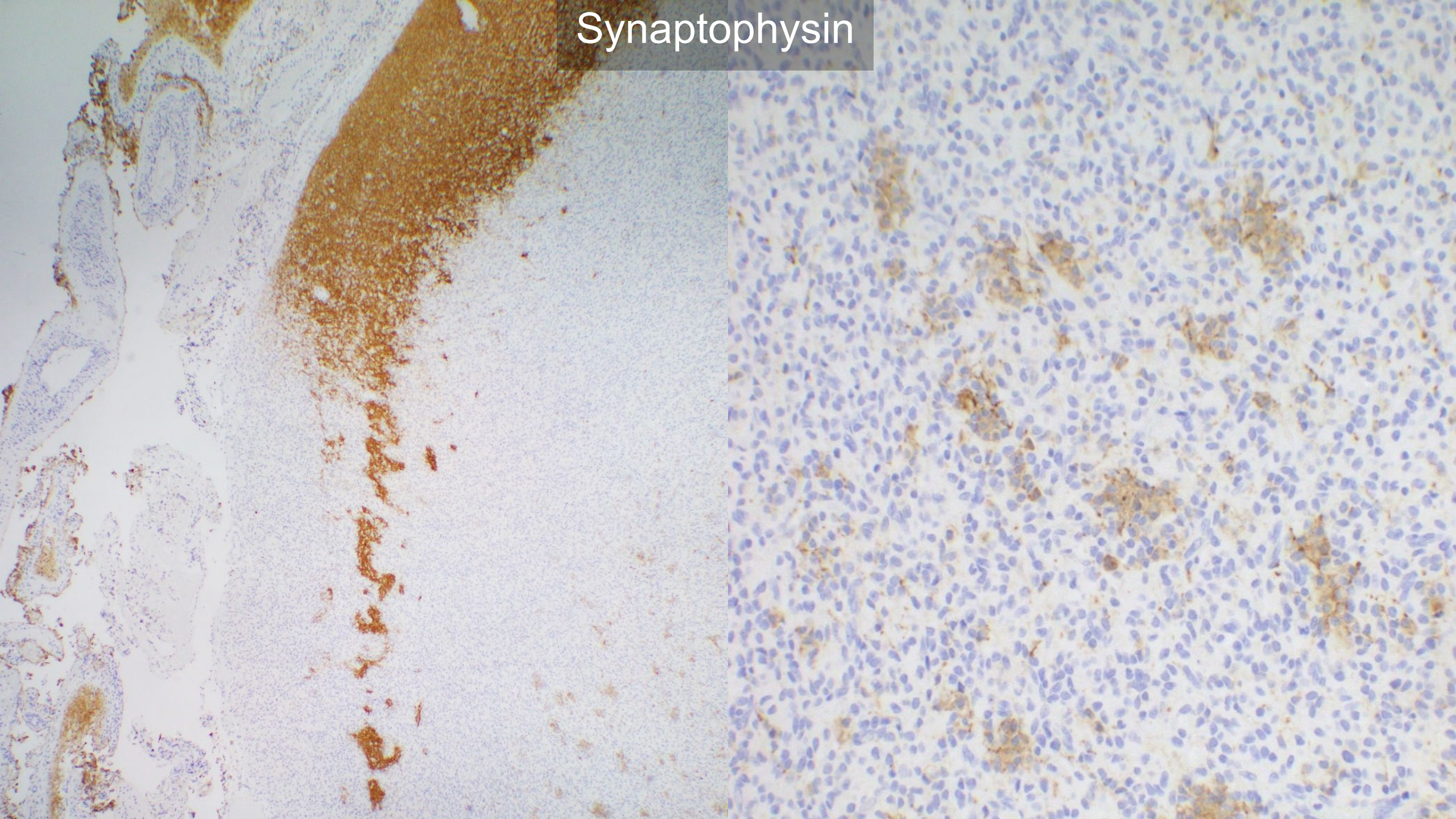


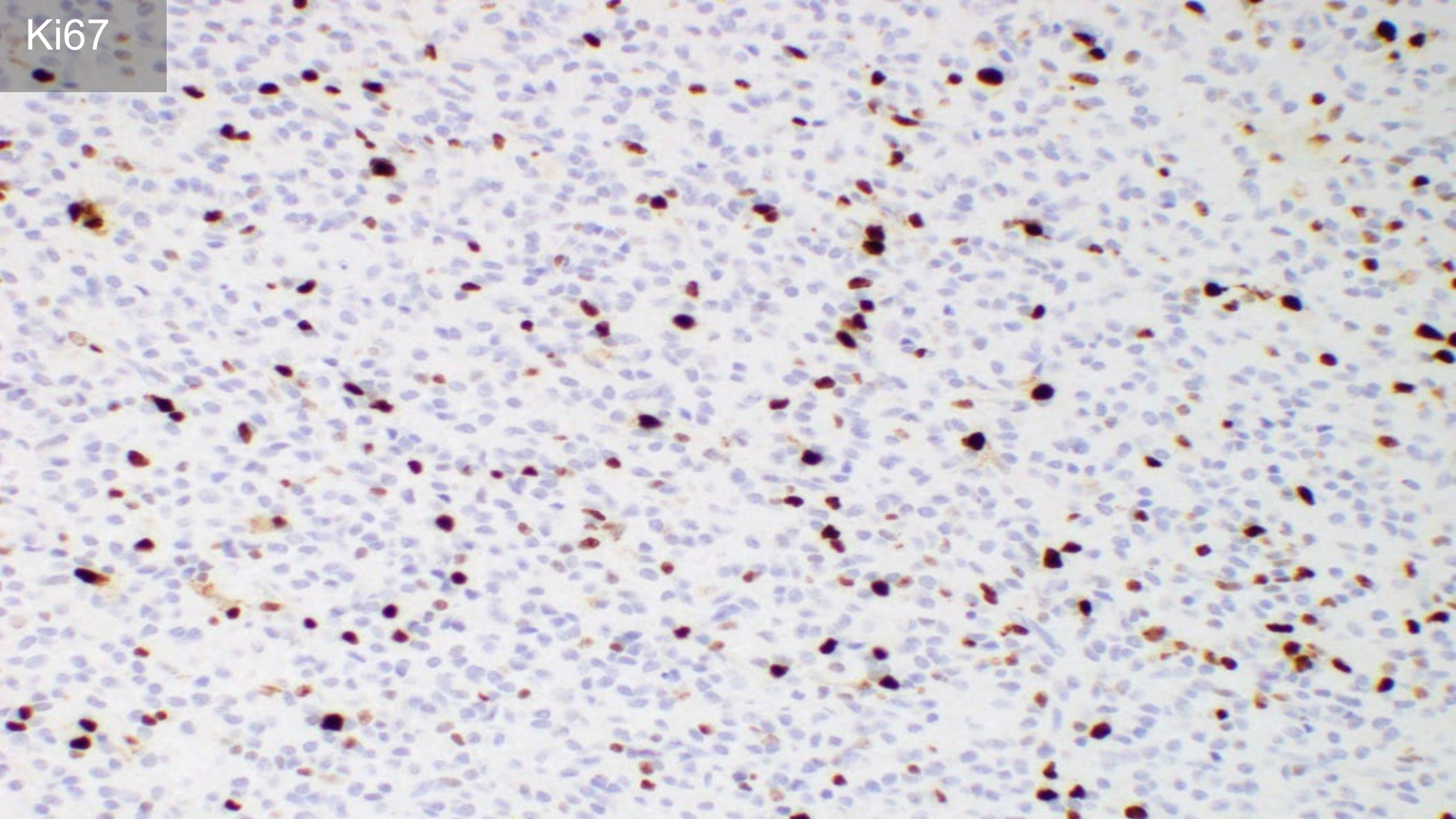




Diagnosis?


GFAP
INI-1


Synaptophysin


Ki67

Molecular Testing Results

- NGS sequencing and fusion panel: ETV6-NTRK3 fusion identified

Methylation sequencing consistent with infant-type hemispheric glioma
(class score 0.996, methylation sequencing, NYU)

ID	Batch ID	Tech	B-number	MP-TN#	Sentrix ID
RD21-883	21-MGDM20	CH	B21-2654	SU21-21249	205549600033_R04C01

Brain Tumor Methylation Classifier

Class Score	Methylation Family	Interpretation
0.996	IHG	Positive
0.003	MTGF_GBM	
0.001	MTGF_PA	
0.001	LGG, SEGA	
0.001	CN	

Subgroup Score	Methylation Subgroup	Interpretation
0.996	IHG	Positive
0.003	GBM, MES	
0.001	LGG, PA/GG ST	
0.001	LGG, SEGA	
0.001	CN	

Final Diagnosis

- **INTEGRATED DIAGNOSIS:** INFANT-TYPE HEMISPHERIC GLIOMA
  - *SUBTYPE: ETV6-NTRK3 fusion positive*

- **HISTOLOGICAL DIAGNOSIS:** HIGH GRADE MALIGNANT NEOPLASM WITH GLIAL DIFFERENTIATION

- **CNS WHO GRADE:** NOT ASSIGNED

SUBTYPE: ETV6-NTRK3 fusion positive

- ETV6 encodes an ETS family transcription factor that regulates hematopoiesis and vascular development.
- NTRK3 encodes the neurotrophic tyrosine kinase-3 receptor and belongs to a family of nerve growth factor receptors whose ligands include neurotrophins.
- ETV6-NTRK3 rearrangements with these breakpoints have been reported, and result in the expression of oncogenic chimeric protein (ETV6-NTRK3).[1] ETV6-NTRK3 has been reported rarely in pediatric non-brainstem high-grade gliomas and pediatric low-grade gliomas.[2-3]

Treatment implications:

- Activating gene fusions involving NTRK genes are associated with response to targeted inhibition.[4-5]
- Identification of this fusion may inform the diagnosis and treatment options.

Patient Update

- Status-post near total gross resection of tumor
- Received vincristine and cyclophosphamide
- Complications of therapy
  - Difficulty feeding requiring NG tube placement
  - Chemotherapy-induced anemia and neutropenia
  - Bacteremia
  - Electrographic and behavioral seizures

- Now 11 months of age – Good energy, activity level, and appetite – continues with chemotherapy regimen.

References

1. Lannon CL, Sorensen PH. ETV6-NTRK3: a chimeric protein tyrosine kinase with transformation activity in multiple cell lineages. Semin Cancer Biol. 2005 Jun;15(3):215-23. doi: 10.1016/j.semcancer.2005.01.003. PMID: 15826836.
2. Wu G, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet. 2014 May;46(5):444-450. doi: 10.1038/ng.2938. Epub 2014 Apr 6. PMID: 24705251; PMCID: PMC4056452.
3. Zhang J, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet. 2013 Jun;45(6):602-12. doi: 10.1038/ng.2611. Epub 2013 Apr 14. PMID: 23583981; PMCID: PMC3727232.
4. Al-Salama ZT, Keam SJ. Entrectinib: First Global Approval. Drugs. 2019 Sep;79(13):1477-1483. doi: 10.1007/s40265-019-01177-y. PMID: 31372957.
5. Gambella A, et al. *NTRK* Fusions in Central Nervous System Tumors: A Rare, but Worthy Target. Int J Mol Sci. 2020 Jan 23;21(3):753. doi: 10.3390/ijms21030753. PMID: 31979374; PMCID: PMC7037946.

Thank You!

- Special thanks to Dr. Matija Snuderl, MD for consultation on methylation studies