AANP 2021
Diagnostic Slide Session Case 8

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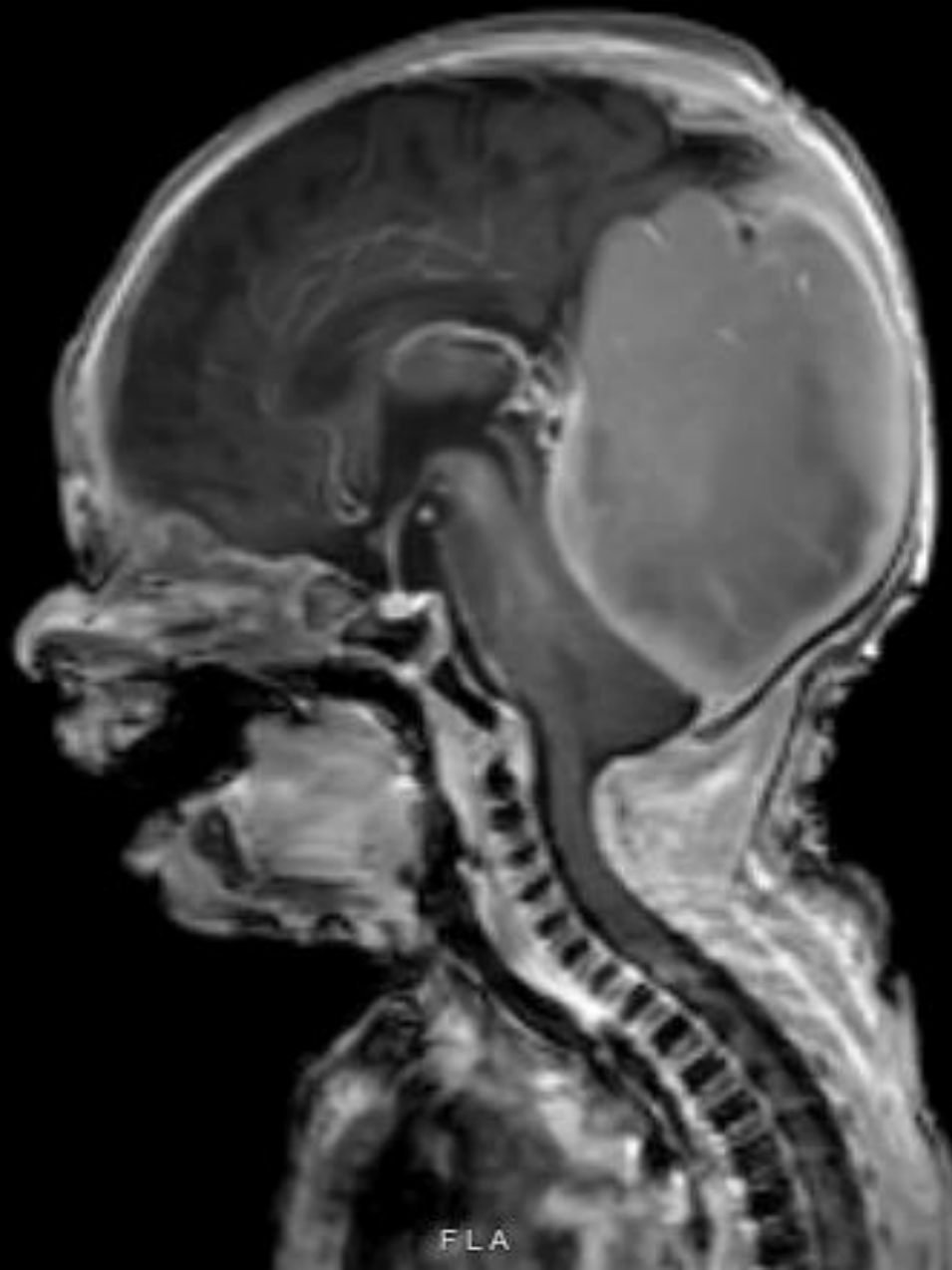
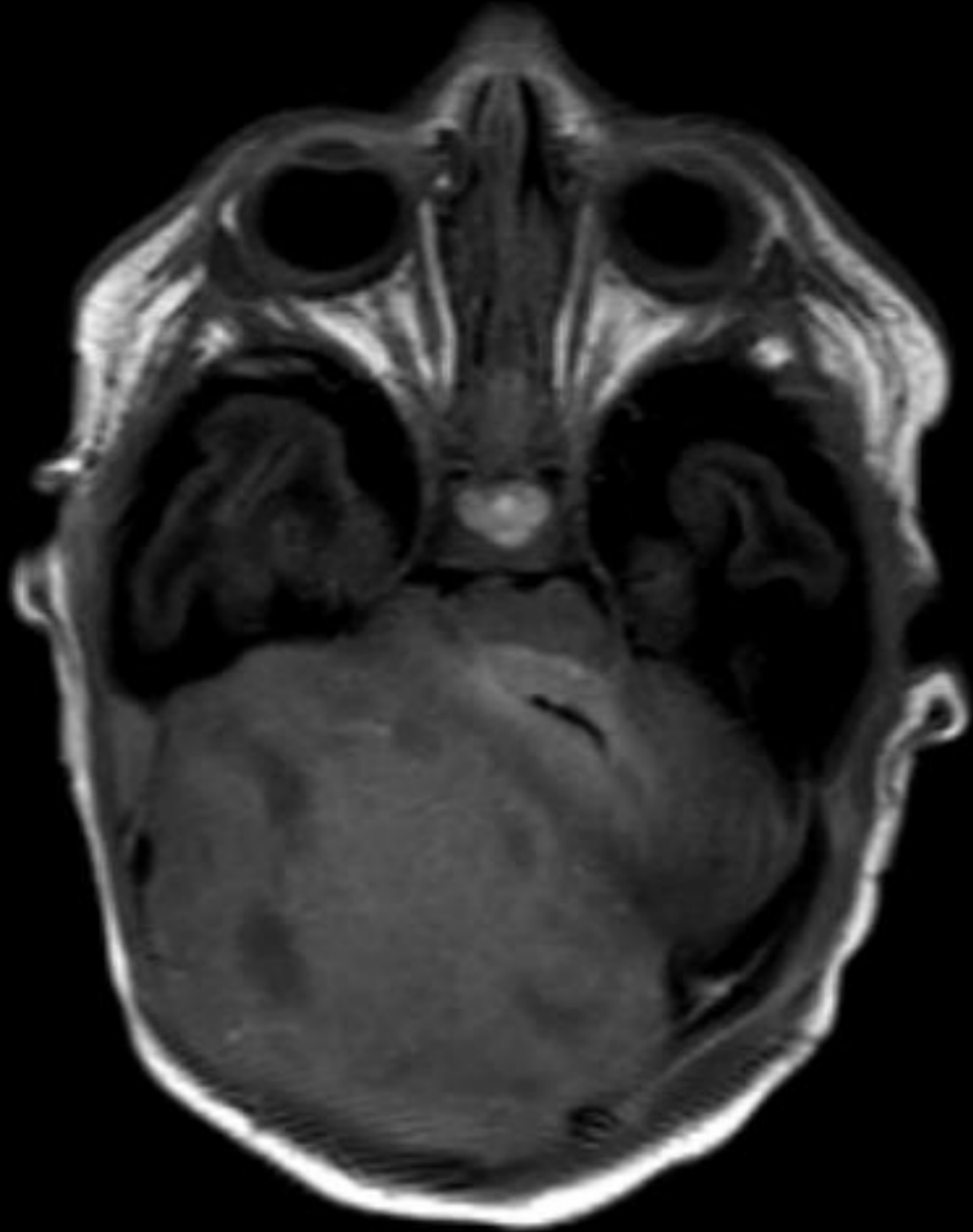
Clinical presentation

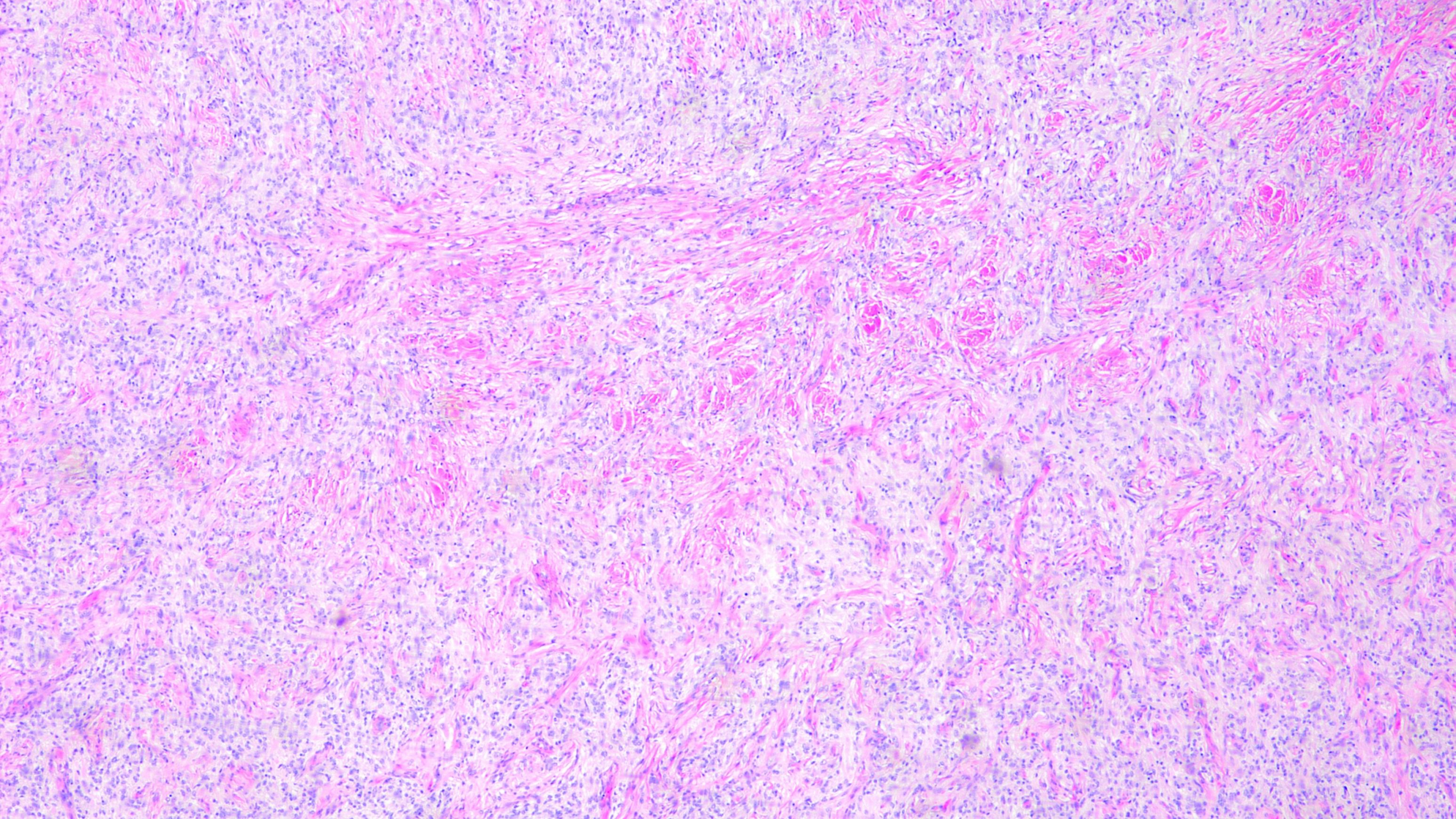
- Infant boy born at gestational age 37 weeks and 2 days with a vascular brain lesion noted on prenatal imaging.
- MR imaging at 1 week of age showed a 7 cm hyper-vascular right parieto-occipital lesion with significant mass effect on the cerebellum and midbrain.
- He underwent preoperative embolization and subtotal resection at 2 weeks of age.
- Intraoperative findings include a large, white, highly vascular tumor occupying the right parieto-occipital space.

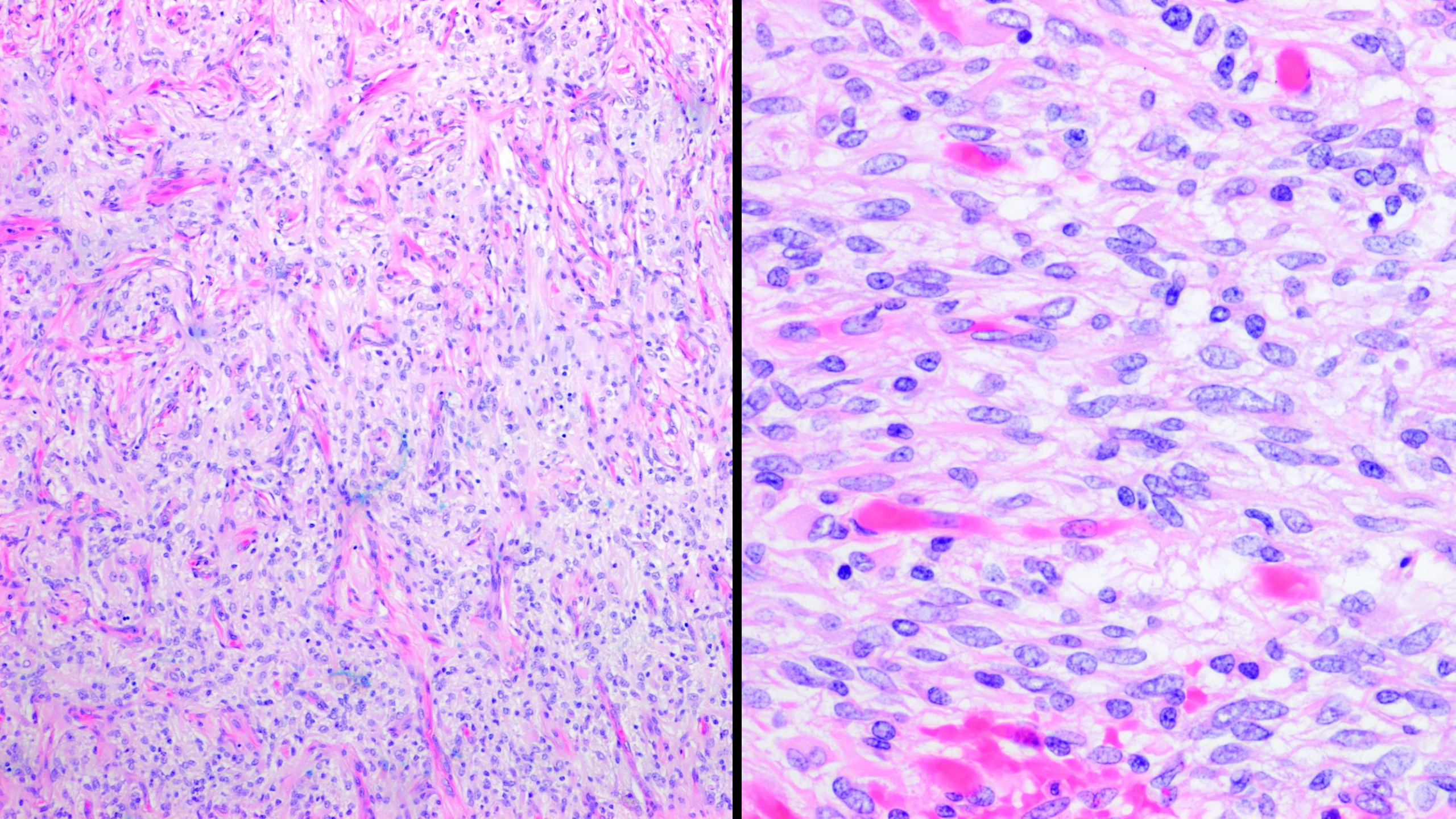
Sagittal T1 post-contrast

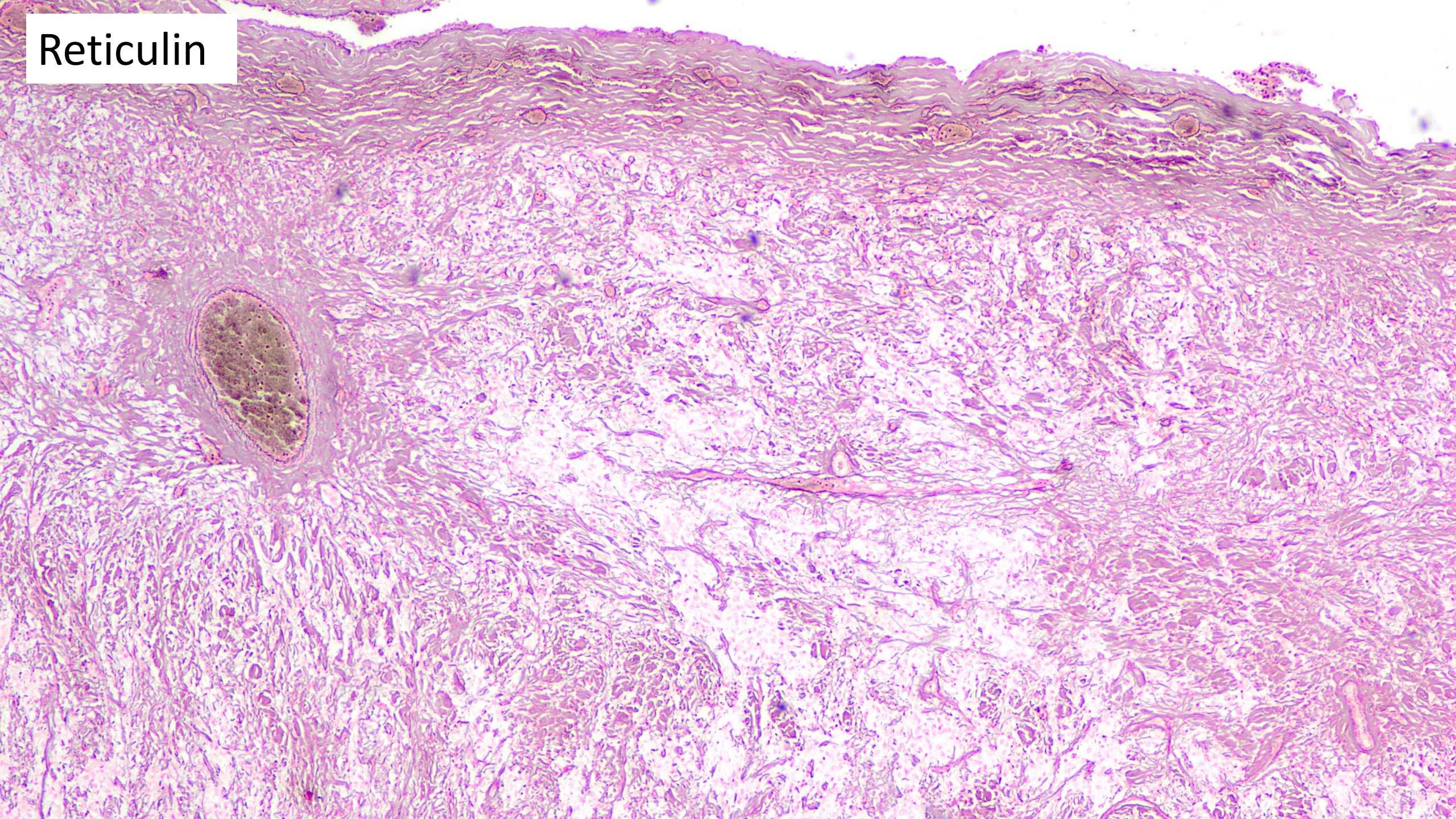


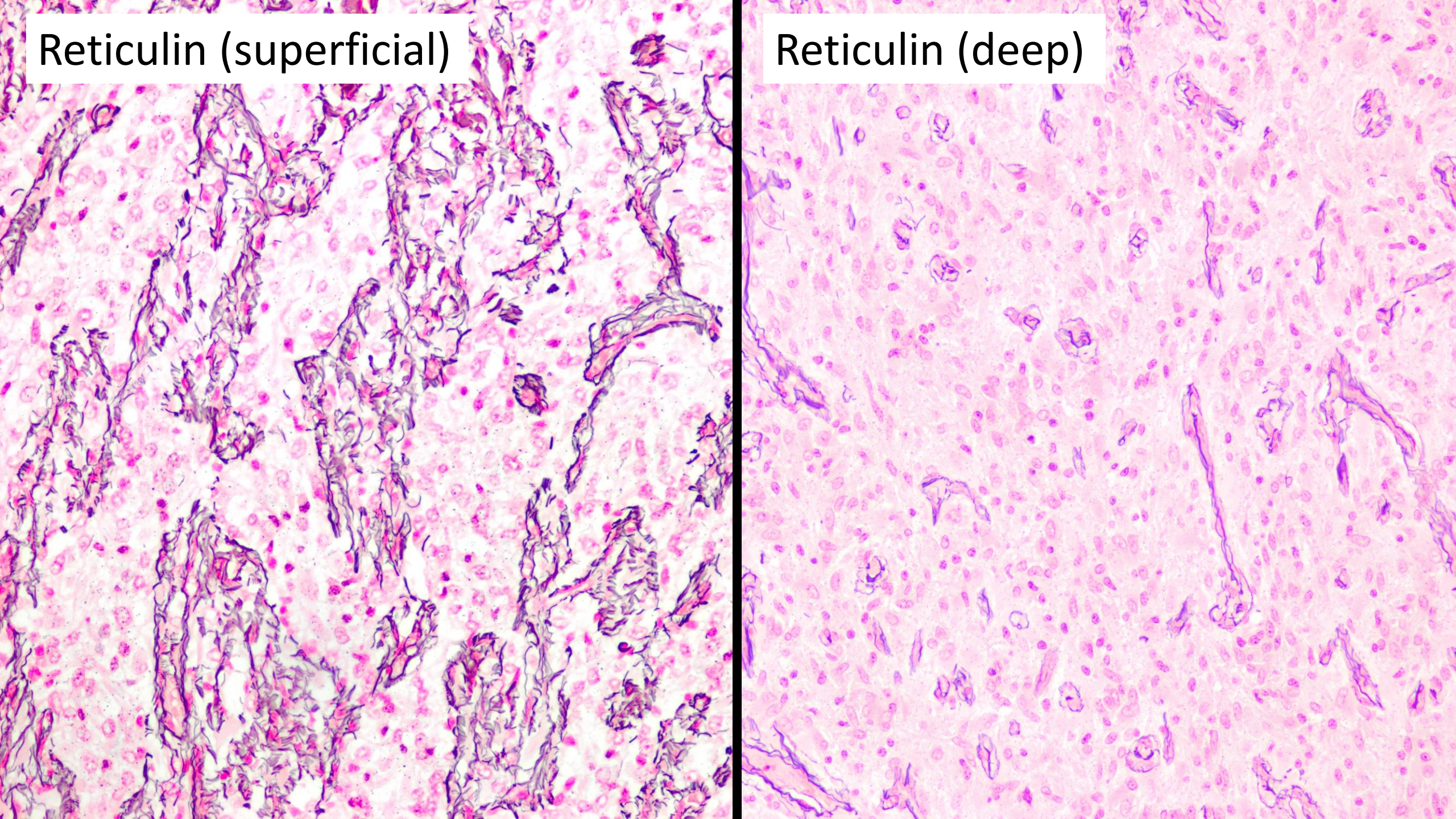
Axial T2 FLAIR



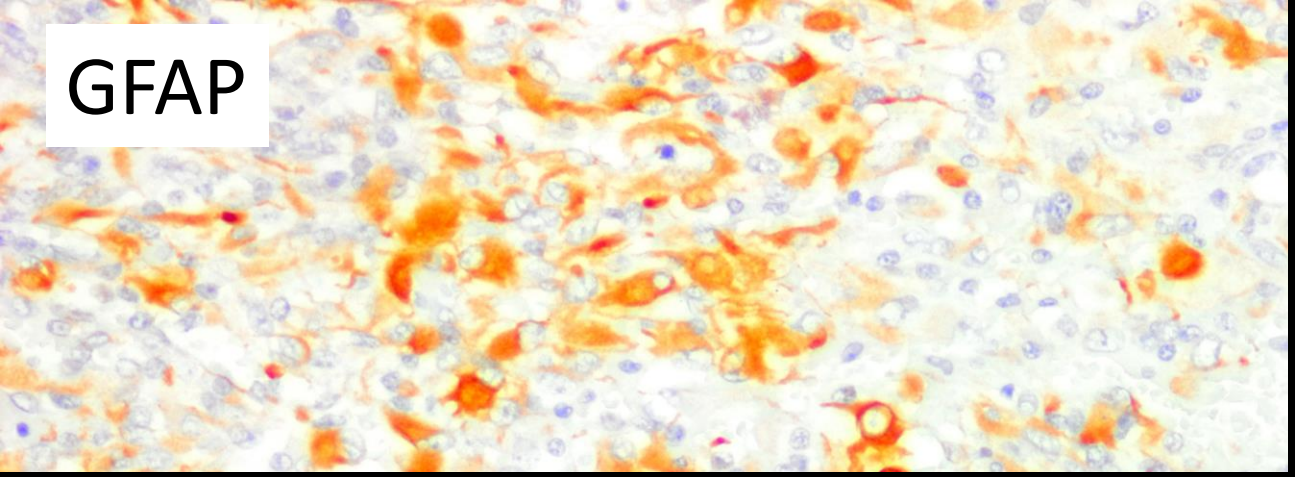


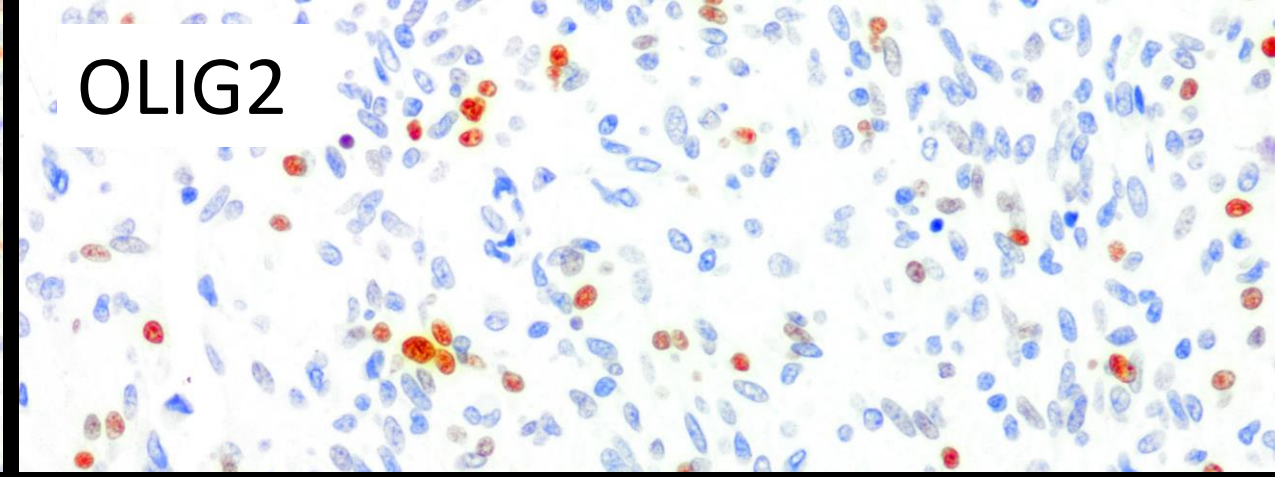


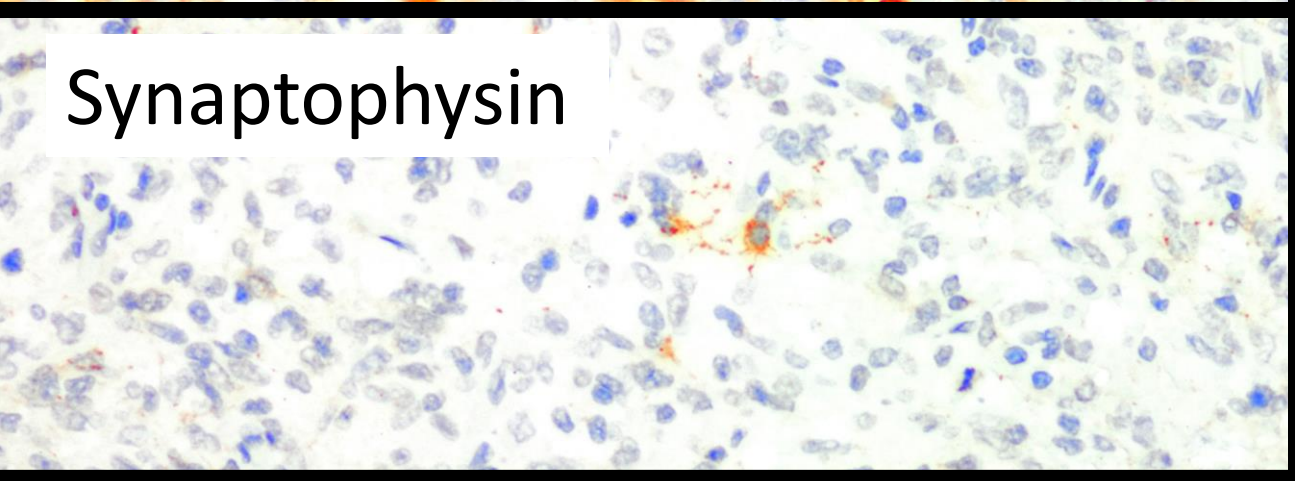

Reticulin

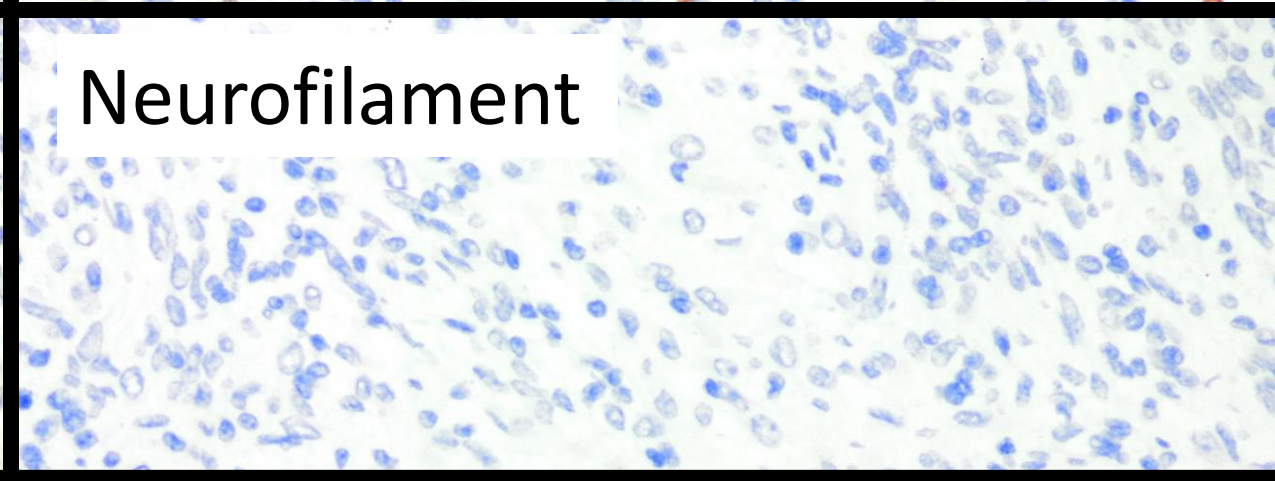

Reticulin (superficial)
Reticulin (deep)

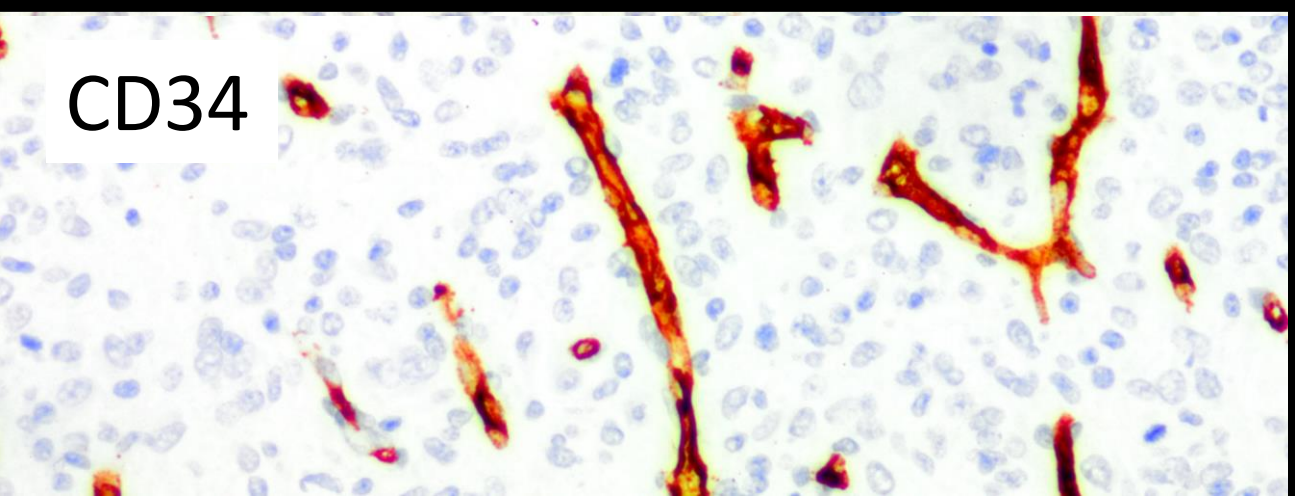
Differential diagnosis?

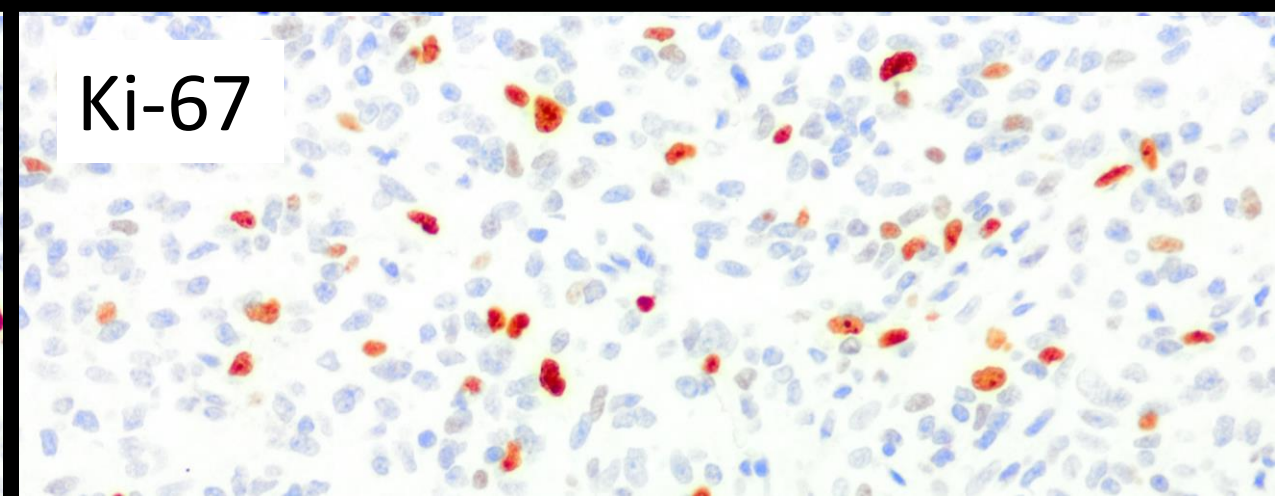

GFAP


OLIG2


Synaptophysin

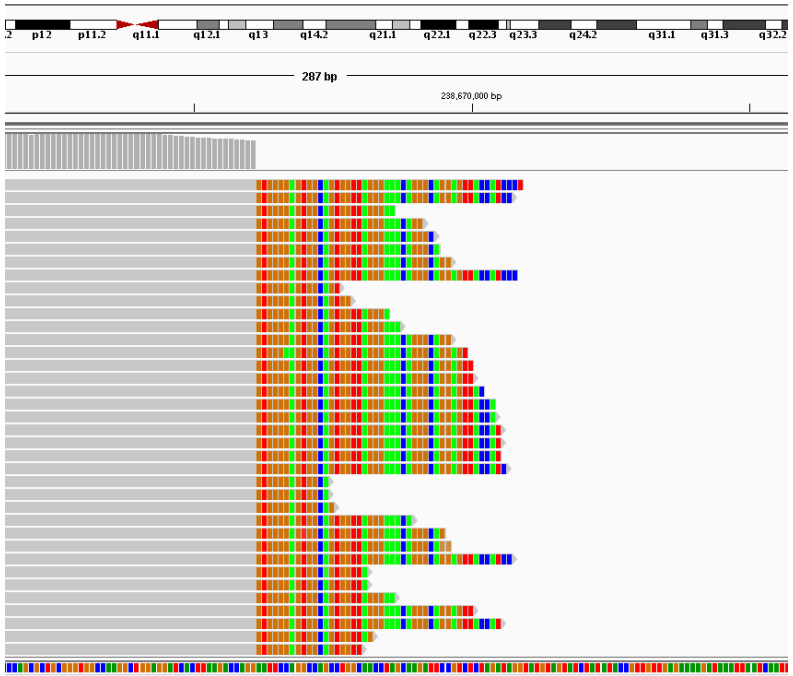

Neurofilament


CD34

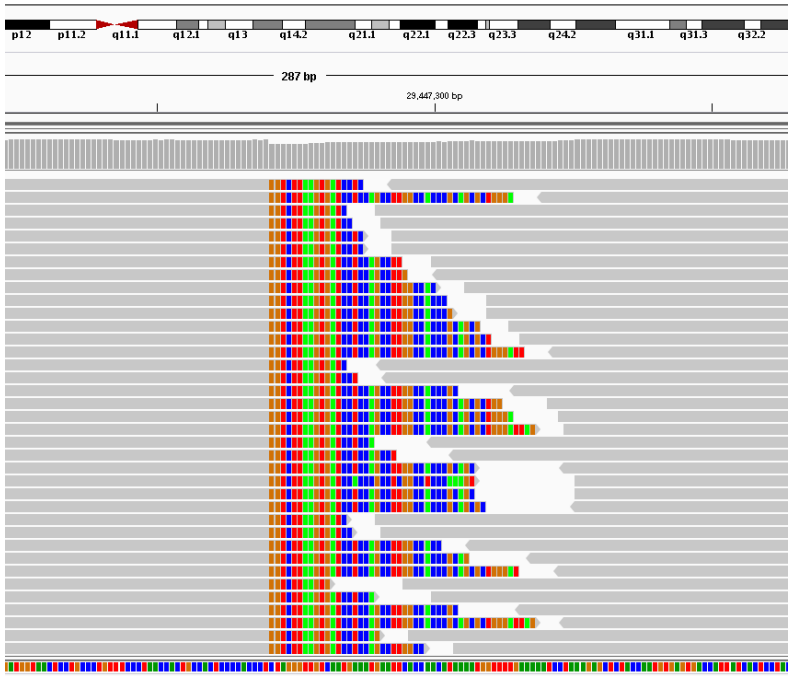

Ki-67

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS				
VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
LRRFIP1-ALK in-frame gene fusion	NM_001137552, NM_004304	Pathogenic	256 over fusion junction	N/A

LRRFIP1 (chr 2q37)



ALK (chr 2p23)



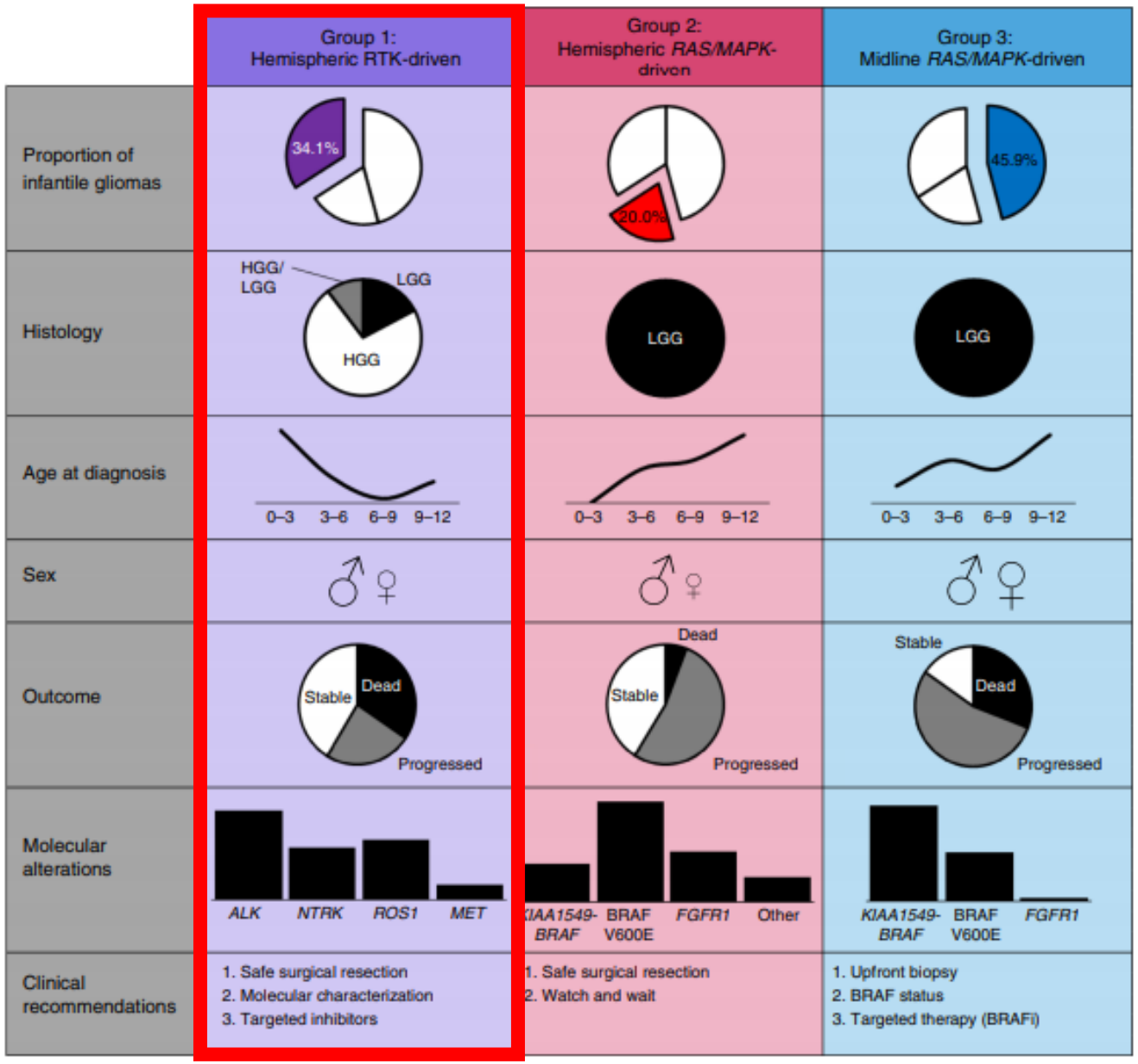
*DNA methylation profiling revealed an epigenetic signature aligning with "**infantile hemispheric glioma**" (DKFZ calibrated score: 0.97)

Integrated diagnosis:
Infant-type hemispheric glioma

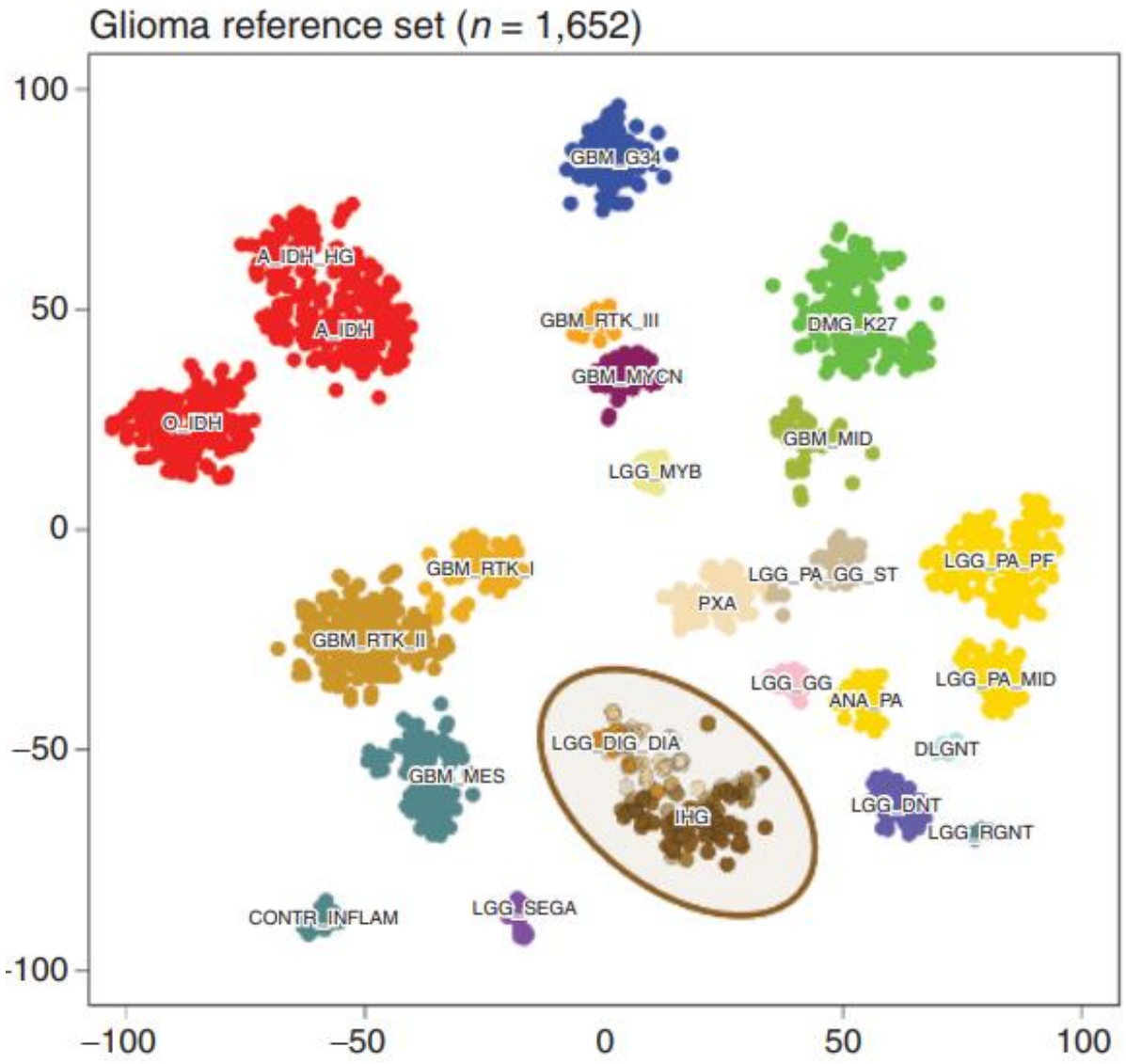
*Infant-type hemispheric glioma represents a new tumor entity in the upcoming 5th edition of the CNS WHO 2021

2.1.2.4: Infant-type hemispheric glioma

Definition
A cerebral hemispheric, cellular, high grade astrocytoma presenting in early childhood, typically with receptor tyrosine kinase (RTK) fusions including those in the NTRK family, *ROS1*, *ALK* or *MET*.



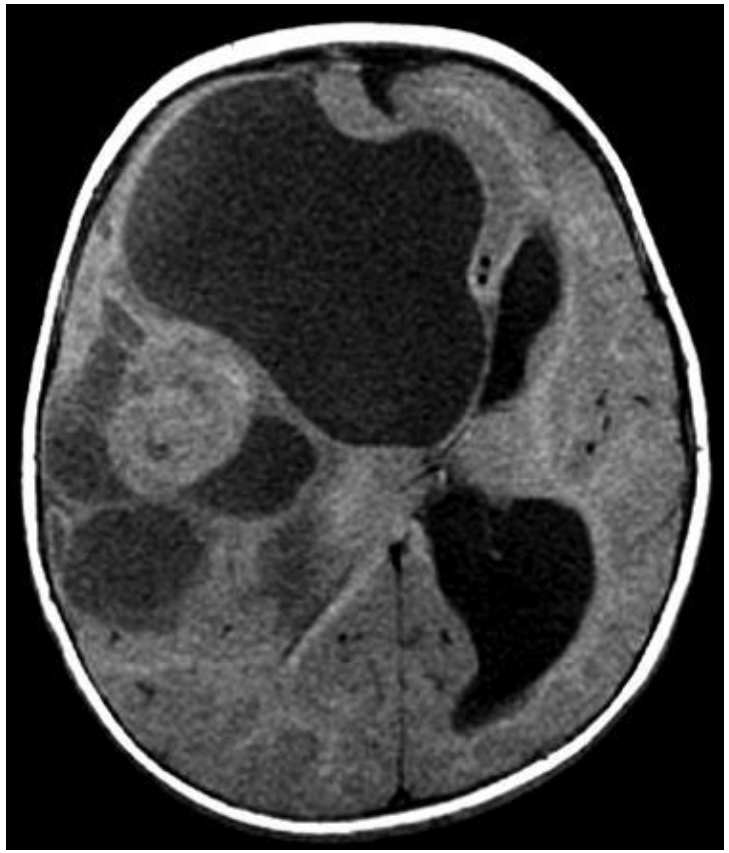
Guerreiro Stucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. *Nat Commun*. 2019;10(1):4343.



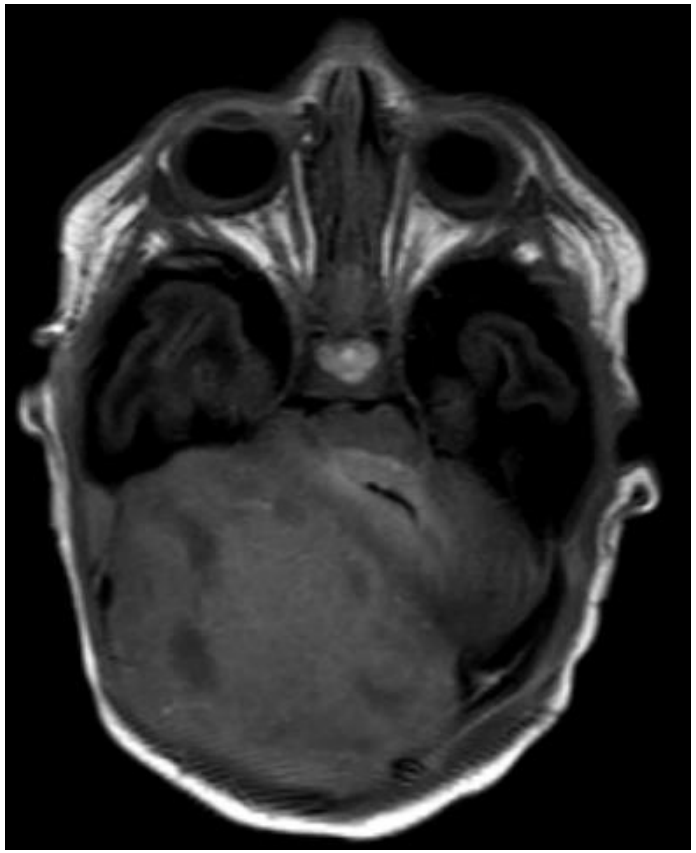
Clarke M, Mackay A, Ismer B, et al. Infant High-Grade Gliomas Comprise Multiple Subgroups Characterized by Novel Targetable Gene Fusions and Favorable Outcomes. *Cancer Discov*. 2020;10(7):942-963.

Differential diagnosis - imaging

- **DIG/DIA** are solid/cystic with large cystic spaces.



- **IHG** are less well-defined but may be more solid/less cystic.



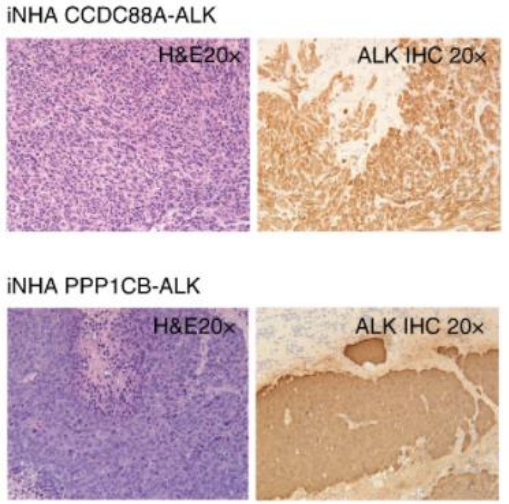
Differential diagnosis - histology

- **DIG/DIA** typically have:
  - prominent desmoplasia and reticulin deposition
  - low Ki-67 labeling usually
  - scattered foci of primitive-appearing cells in some cases
- **IHG** are less well-defined but often:
  - appear histologically high-grade
  - show an elevated Ki-67 labeling
  - can have palisading necrosis and microvascular proliferation

*This tumor had a mostly circumscribed growth pattern devoid of entrapped axonal processes.

(are infant-type hemispheric gliomas “diffuse/infiltrative” gliomas?)

* This tumor demonstrated dural invasion, mimicking the desmoplasia associated with DIG/DIA.



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Ancillary testing:

- Next generation sequencing can help to differentiate DIG/DIA (enriched for *BRAF* mutations, particularly non-p.V600E variants) from IHG (enriched for *ALK/ROS/MET/NTRK* fusions).
- DIG/DIA and IHG have distinct epigenetic signatures and DNA methylation profiling can also be helpful as an ancillary diagnostic tool.

References:

- Koelsche C, Sahm F, Paulus W, et al. BRAF V600E expression and distribution in desmoplastic infantile astrocytoma/ganglioglioma. *Neuropathol Appl Neurobiol*. 2014;40(3):337-344. doi:10.1111/nan.12072
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