DSS 2017-9

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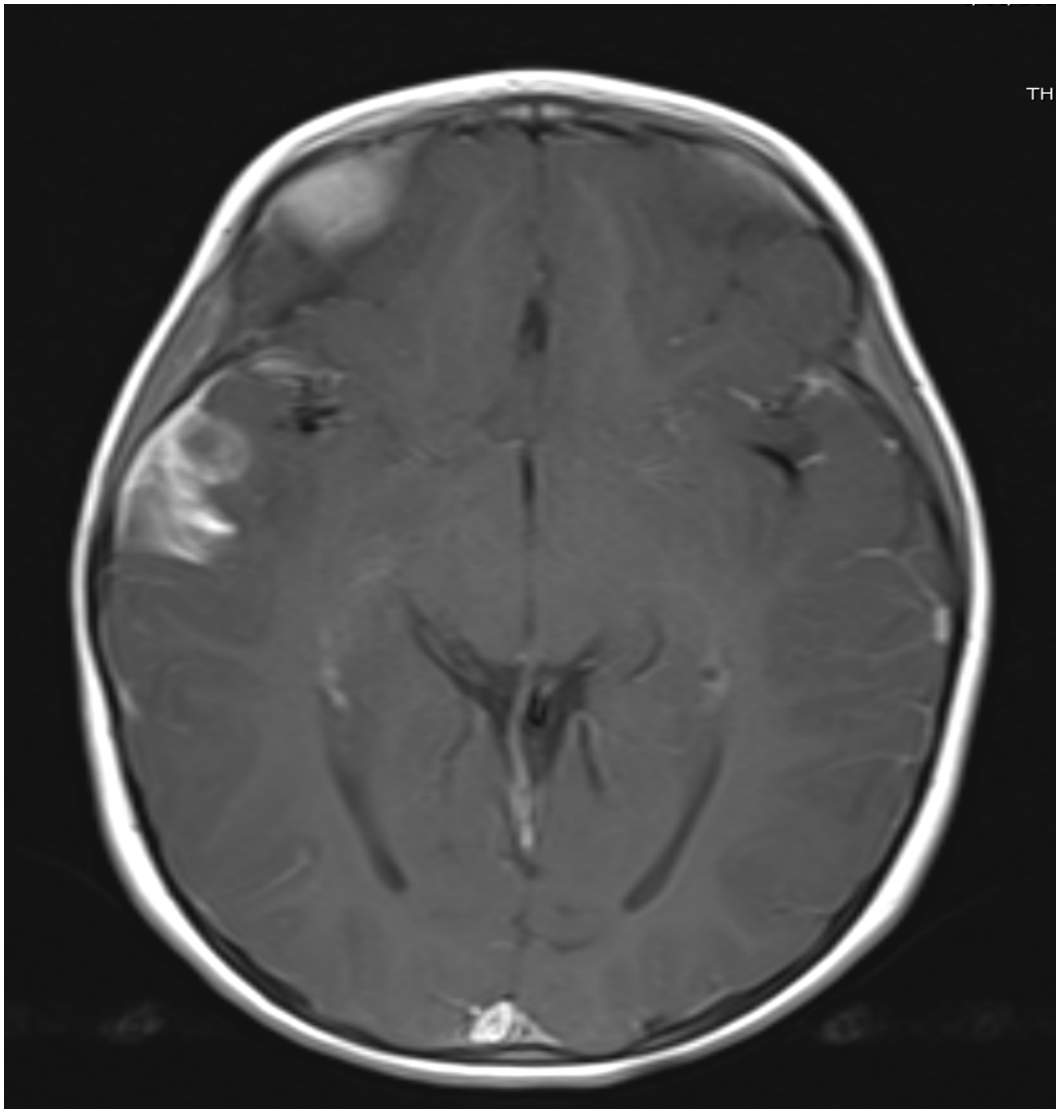
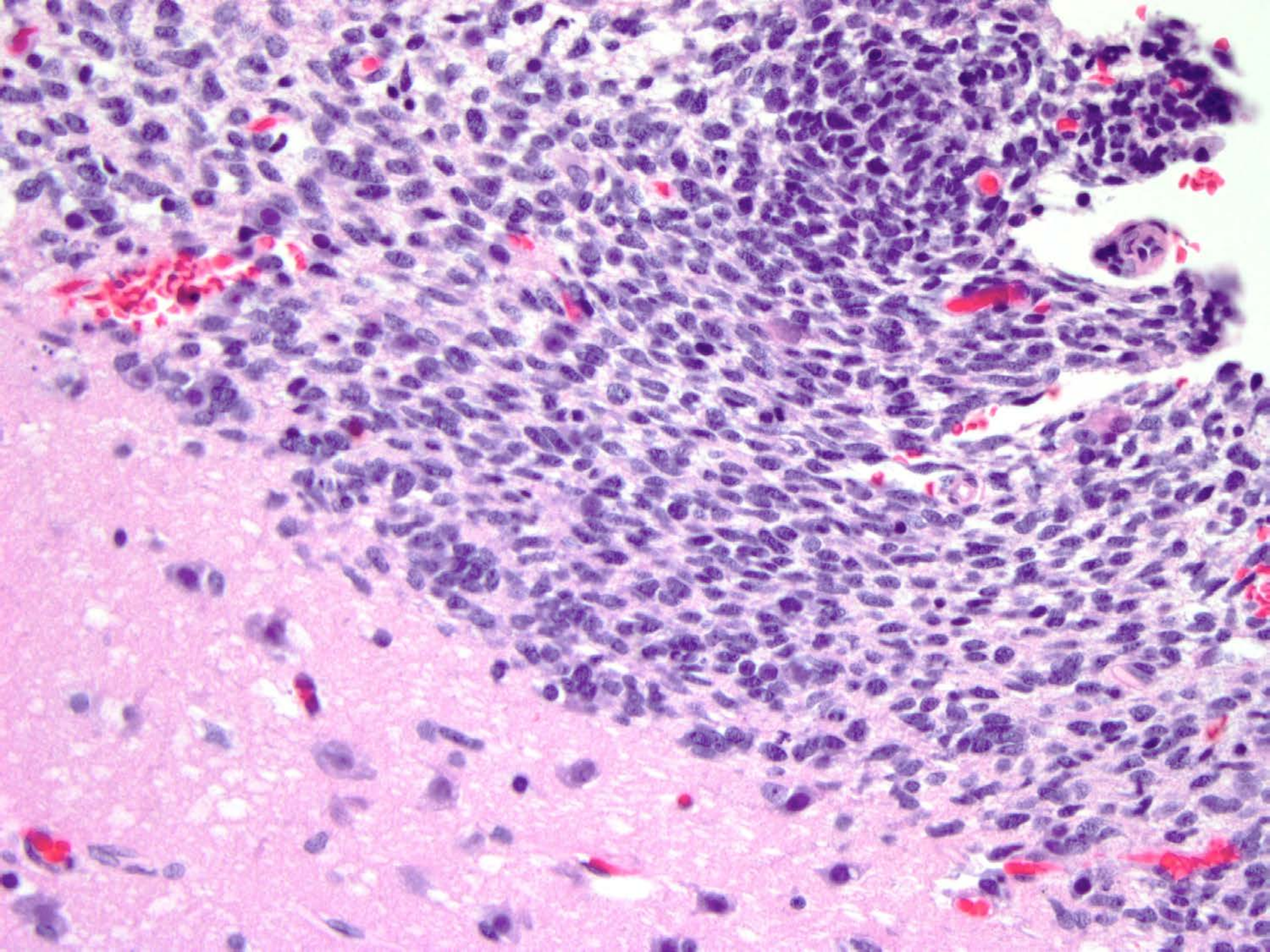
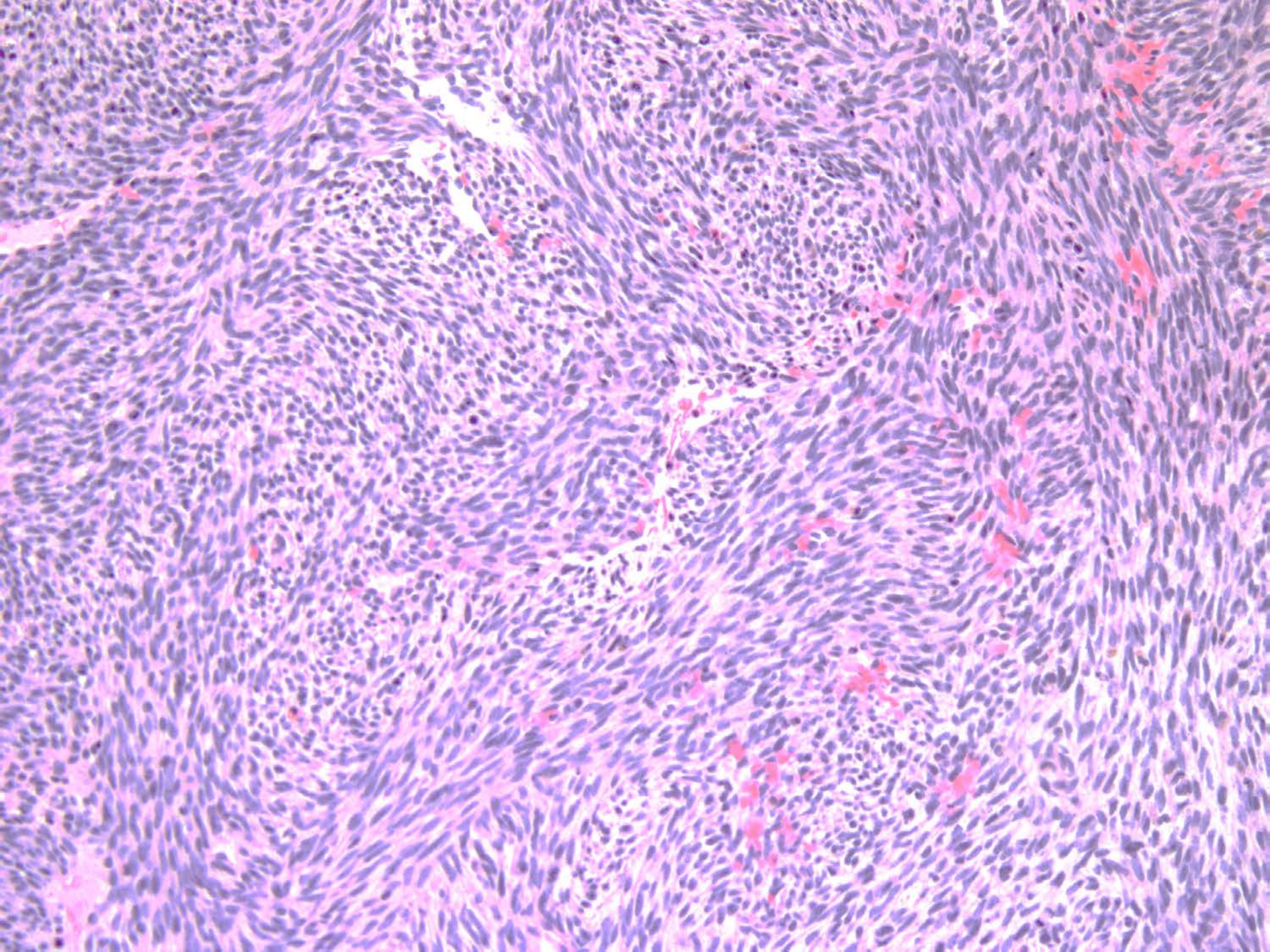
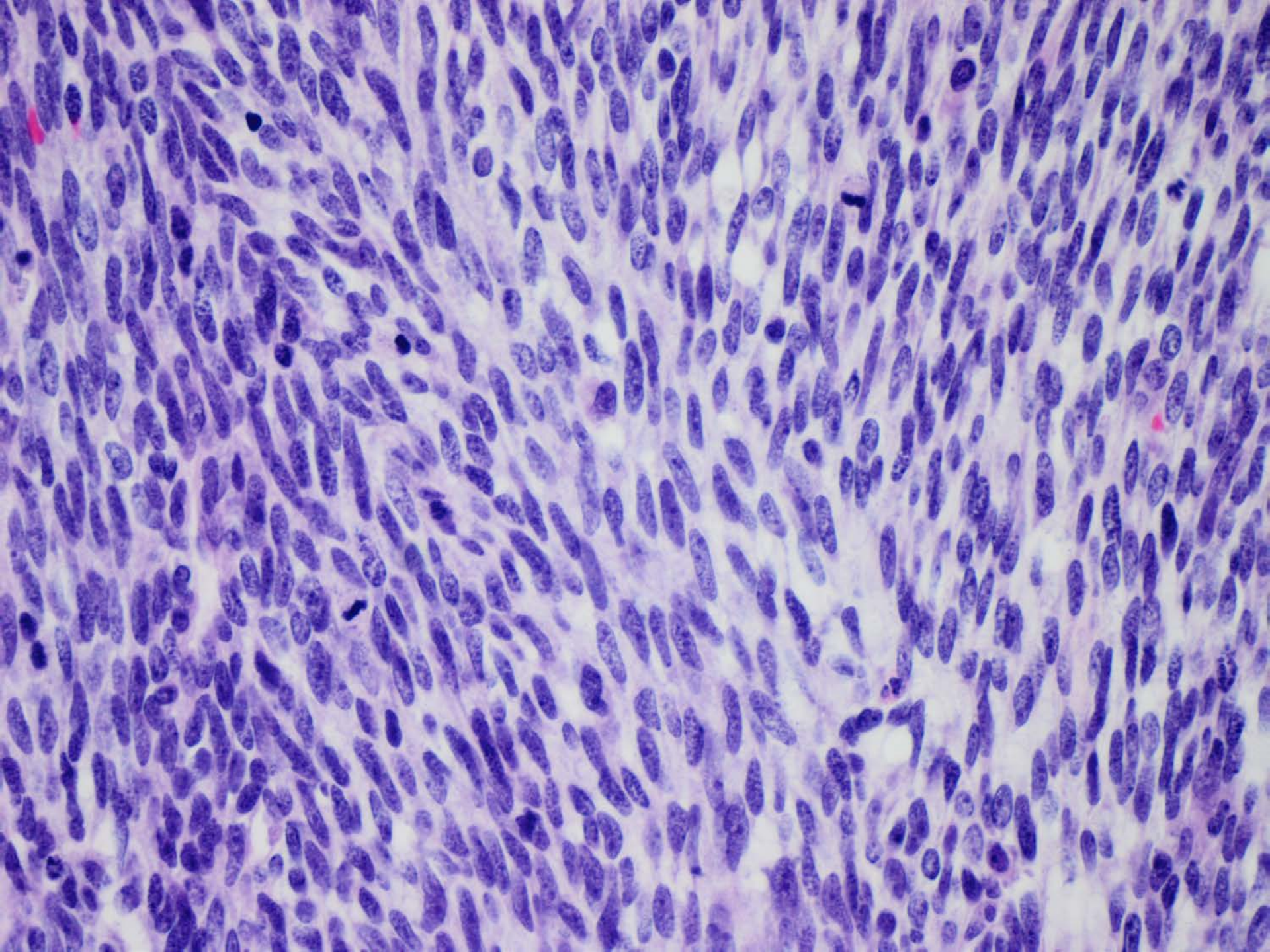
Boston Children's Hospital

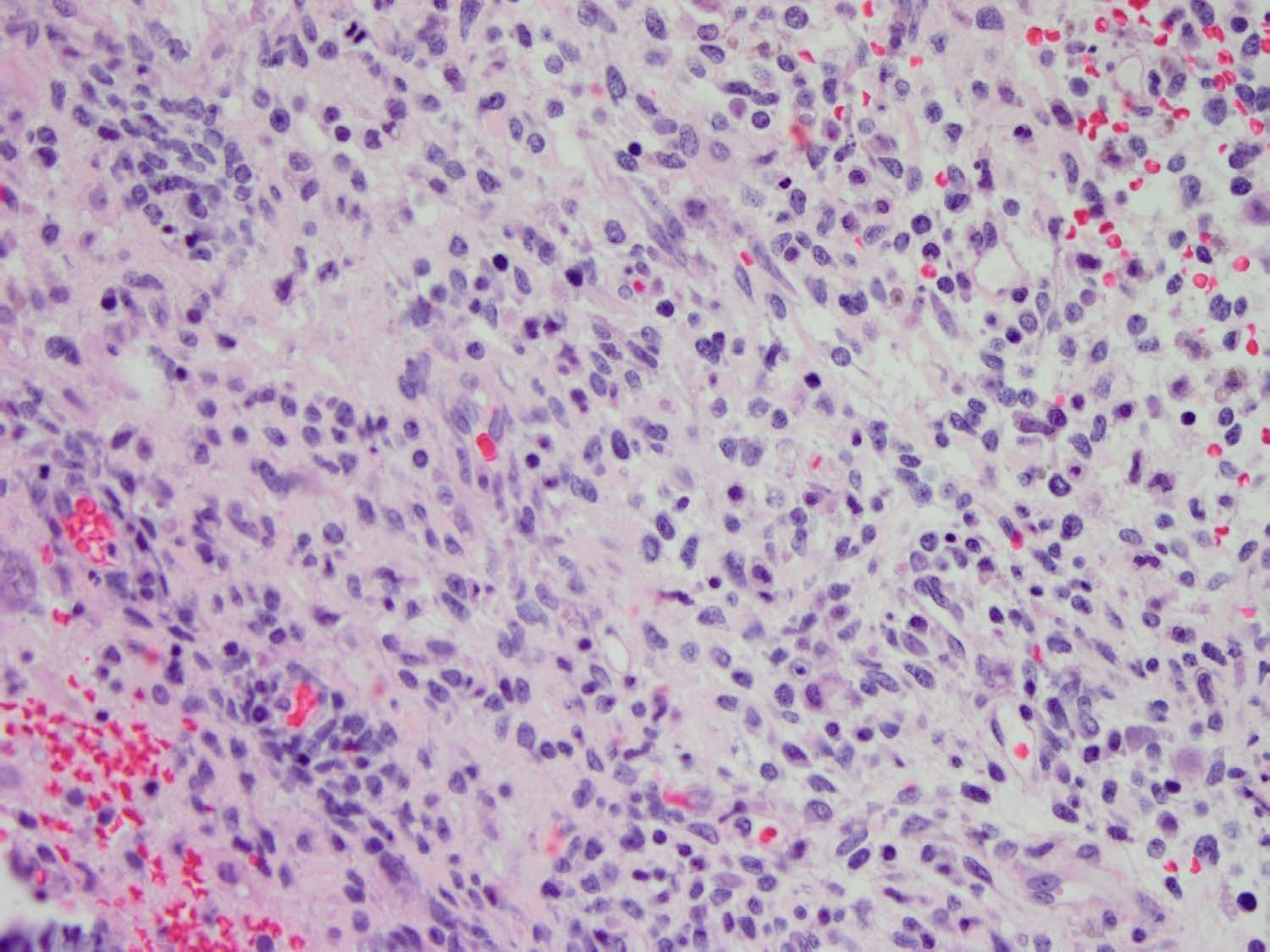
3 year-old girl with a short history of headaches









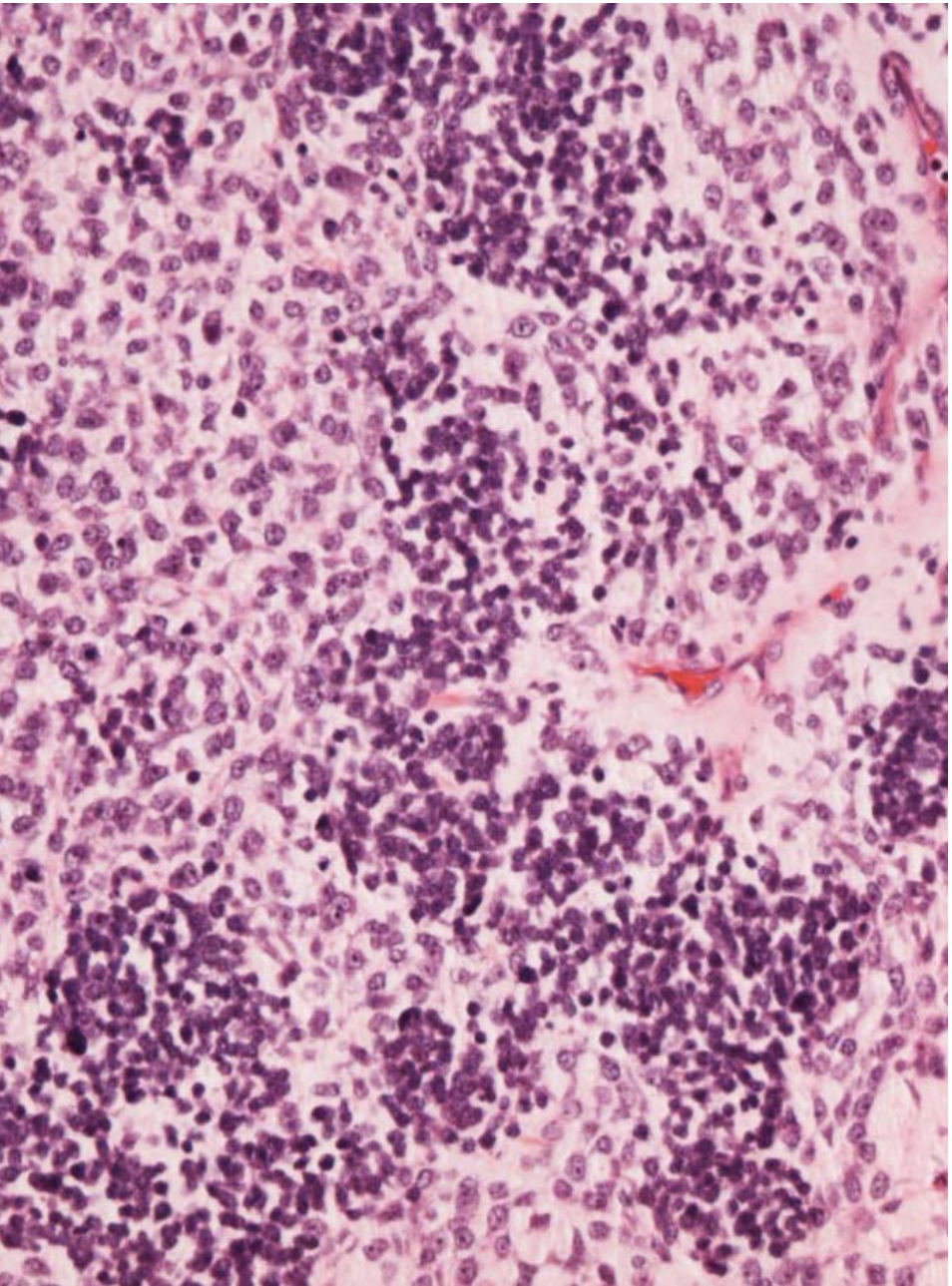


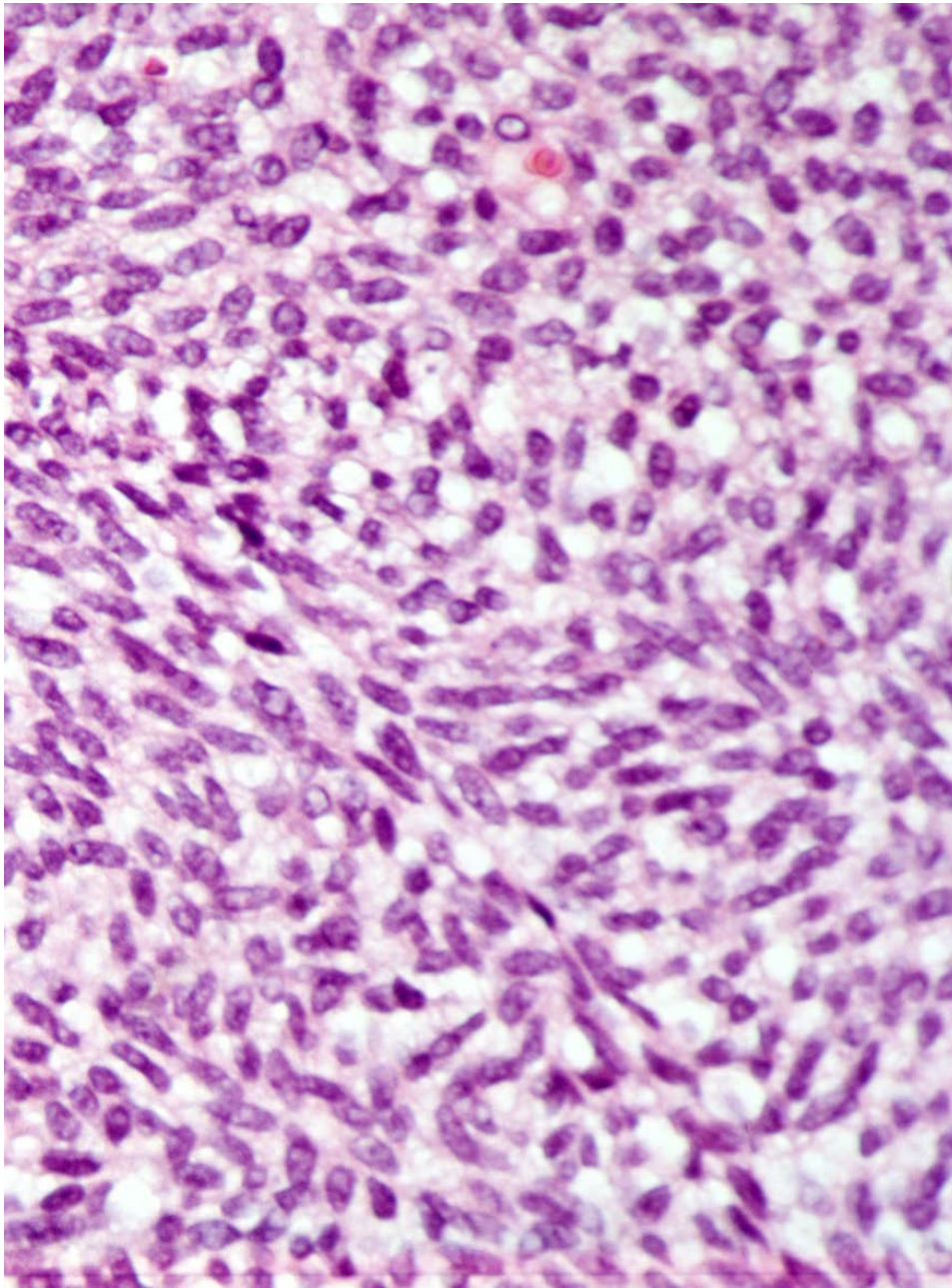
Differential diagnosis?
Immunohistochemical stains?
Molecular tests?
Final diagnosis?

Differential Diagnosis

High-grade glioma/gliosarcoma
Anaplastic meningioma
Malignant hemangiopericytoma
Rhabdoid tumor
Synovial sarcoma
Malignant peripheral nerve sheath tumor
Malignant triton tumor
Rhabdomyosarcoma
Ewing family/Ewing-like sarcoma
Leiomyosarcoma
….”it resembles solid pleuropulmonary blastoma – a DICER1 associated tumor?”

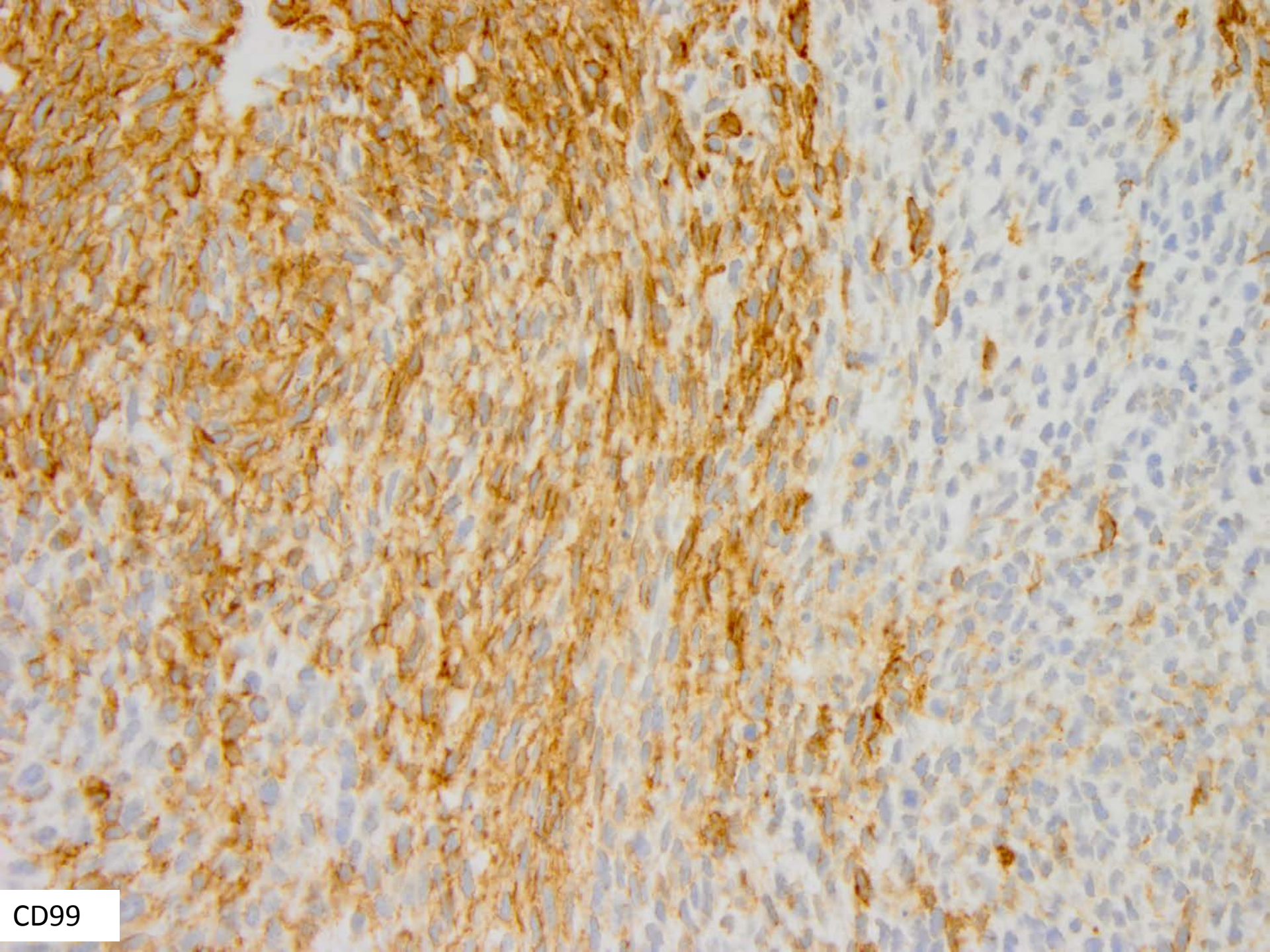
Pleuropulmonary blastoma type 3 (another patient)

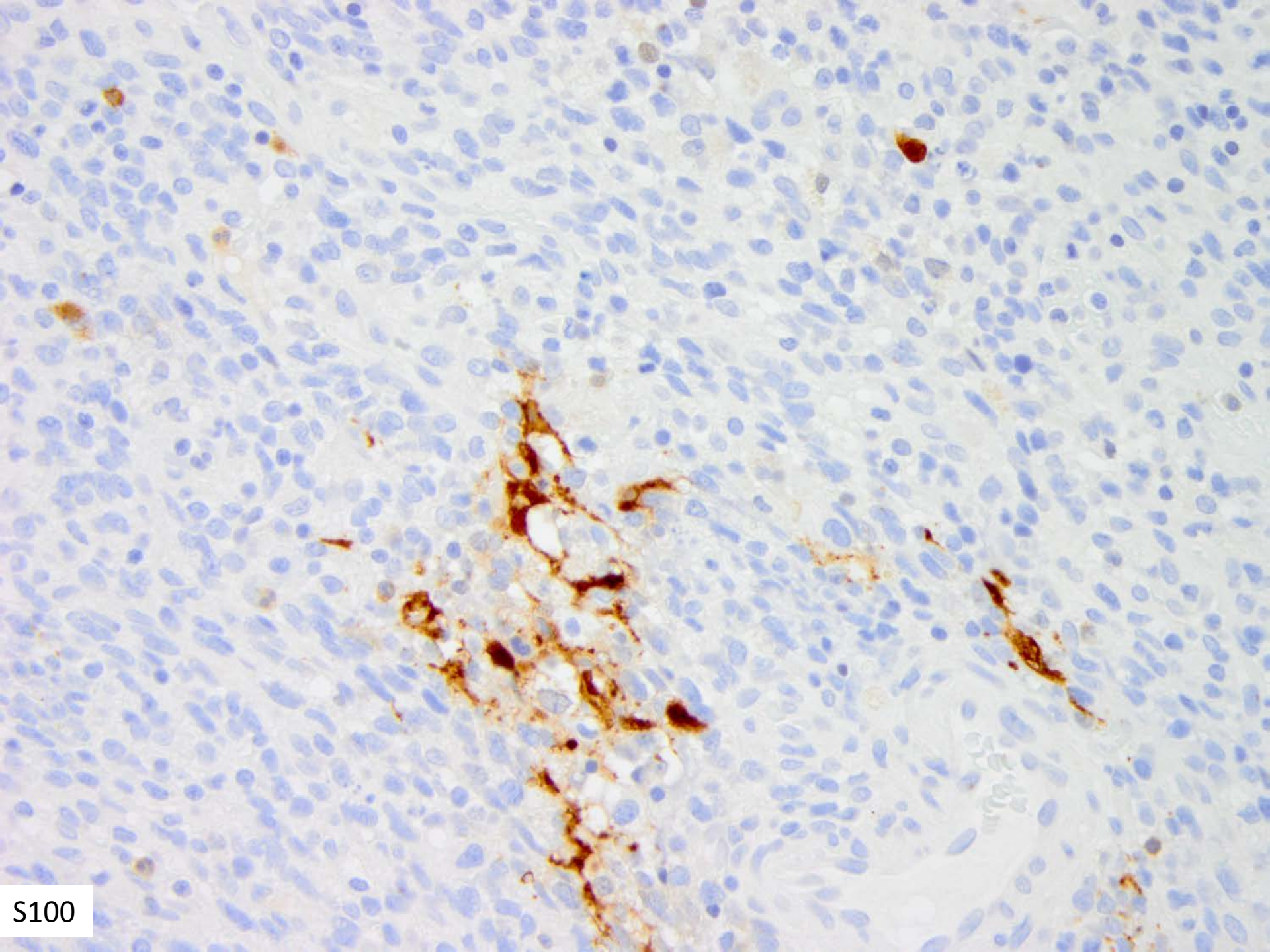


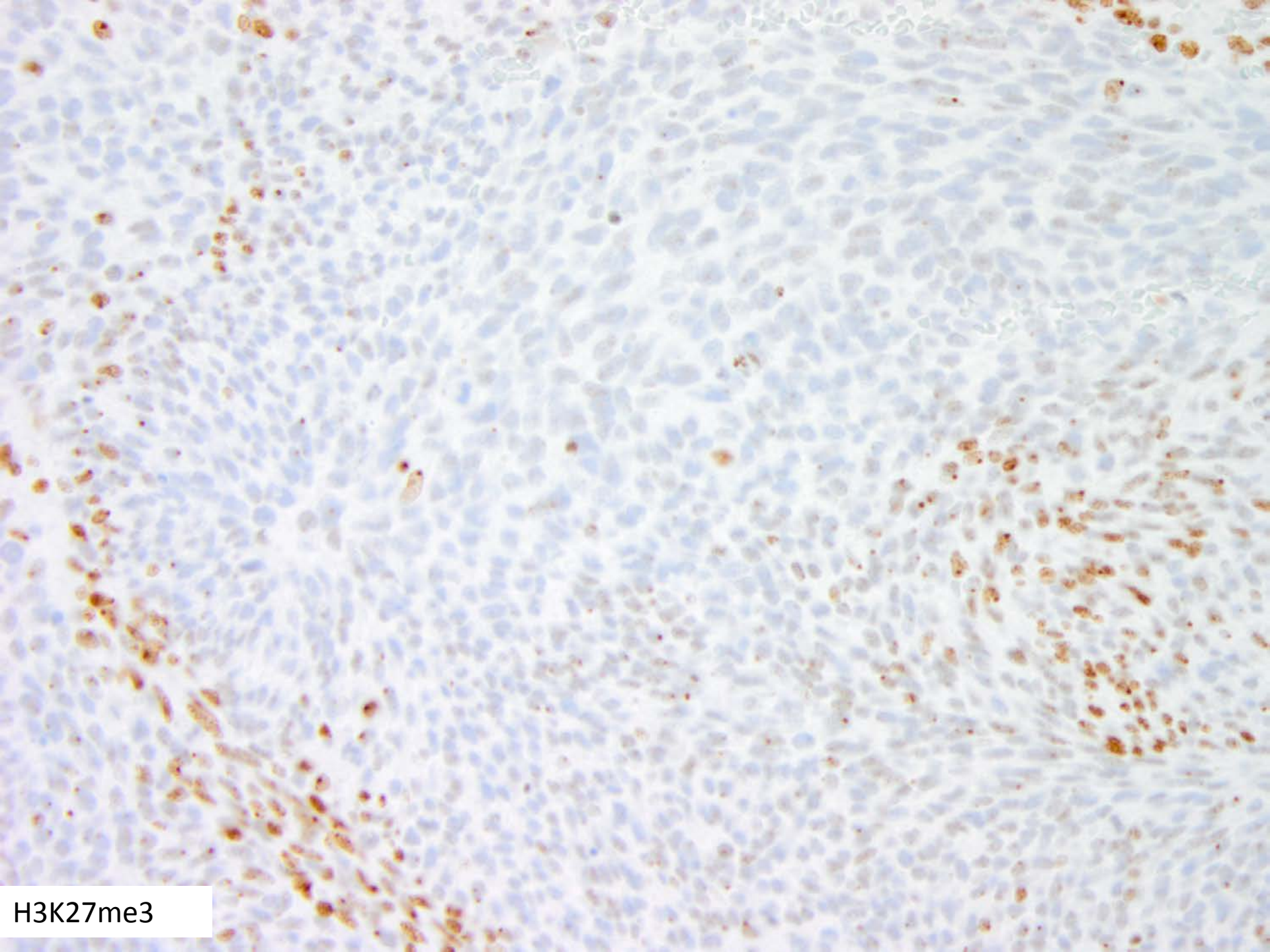


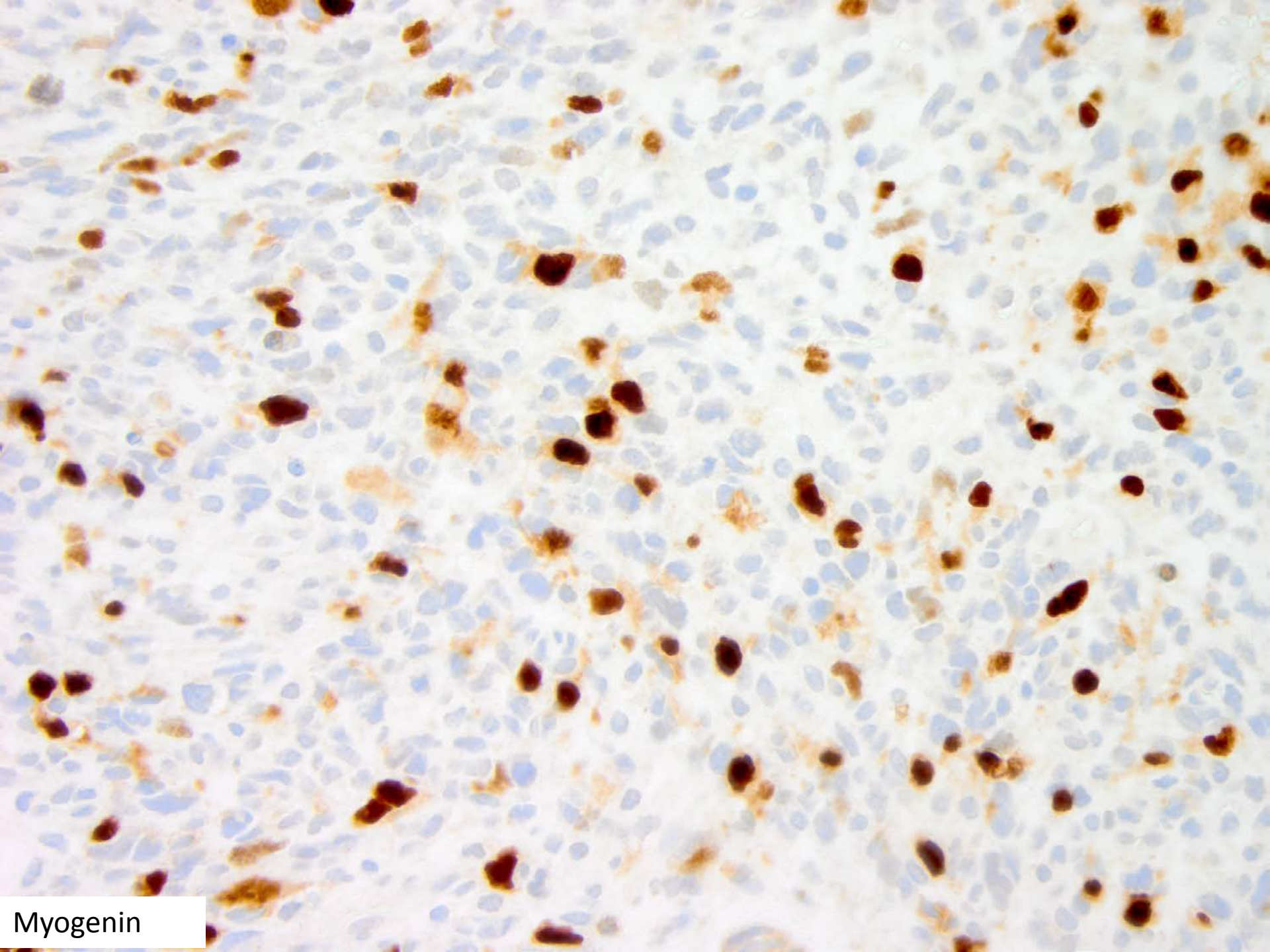
The tumor is negative for:

- GFAP
- OliG 2
- Synaptophysin
- SOX 2
- SOX10
- CD34
- TLE 1
- STAT 6
- MNF116
- CAM5.2
- EMA
- Somatostatin receptor 2A
- ALK1
- BRG1 (SMARCA4)
- INI1 (SMARCB1)


CD99


S100


H3K27me3


Myogenin

- Array CGH (not specific for a particular tumor type):
  - 103.9Mb single copy gain of 1q
  - polysomy of chromosome 2
  - 94.5 Mb single copy deletion of 6q
  - 31.8 Mb single copy 12p

- Copy number changes described in MPNST/MTT (Brekke HR, J Clin Oncol. 2010 Mar 20;28(9):1573-82) :
  - gains of 8q, 17q, 7p, 16p
  - losses of 1p, 3p, 9p, 10q, 11q, 16q, 17p, 22q, Xp

Diagnosis:

Right temporal hemorrhagic lesion, gross total resection:

- High-grade malignant spindle cell tumor with rhabdomyosarcomatous differentiation

OncoPanel (Illumina HiSeq):

-DICER1 c.5125G>A (p.D1709N) in 43% of reads

-DICER1 c.904-1G>A () in 42% of reads

-KRAS c.35G>A (p.G12D) in 69% of reads

Note:

•DICER1 c.5125G>A (p.D1709N) :

- Hotspot variant (Brennan M et al. F1000 Research 2015, 4-217)
- Deregulates miRNA production and promotes cell growth and differentiation

DICER1 c.904-1G>A ():

- Predicted to eliminate the acceptor site at 3' end of intron 9 and to abrogate or reduce the activity of the DICER1 protein product.

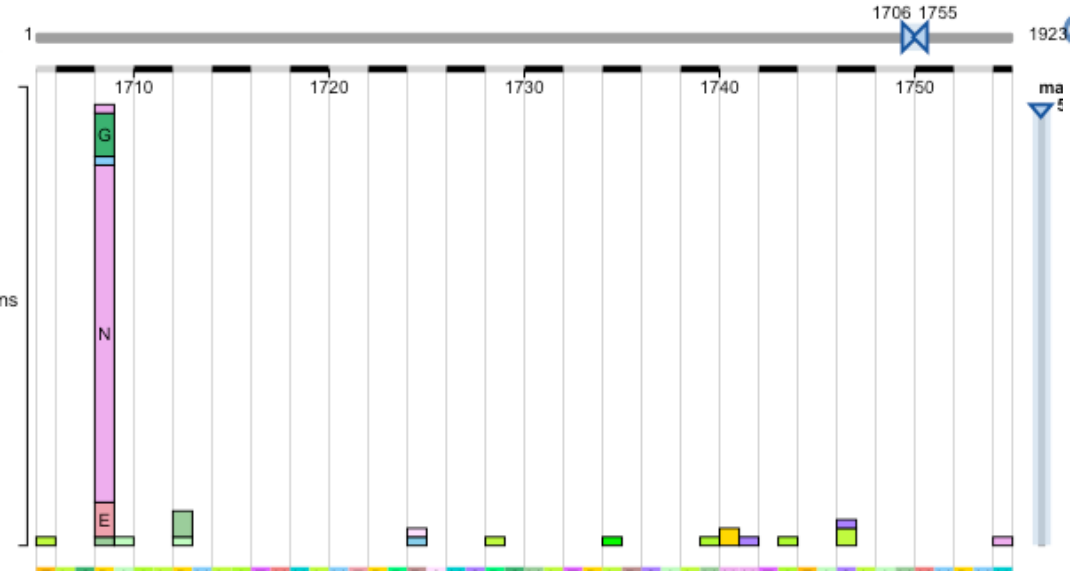
•KRAS c.35G>A (p.G12D):

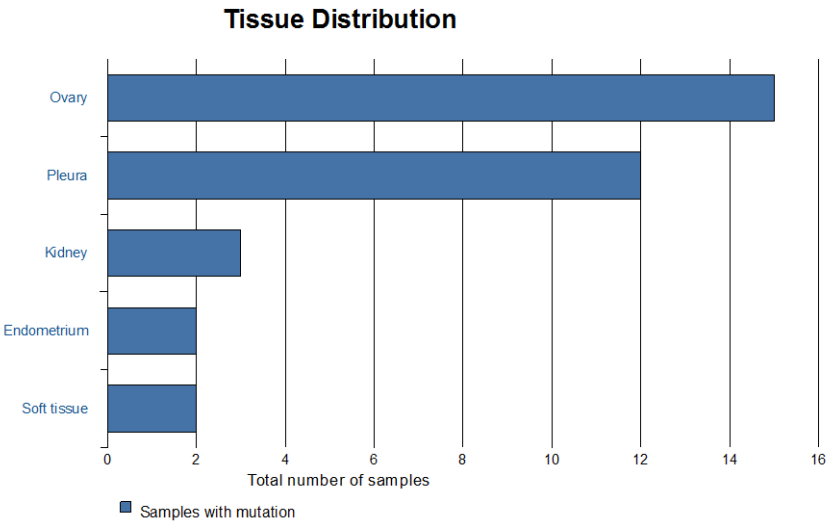
- Hotspot mutation, known to be activating (Rachagani S. et al. Br J Cancer. 2011 Mar 15;104(6):1038-48)

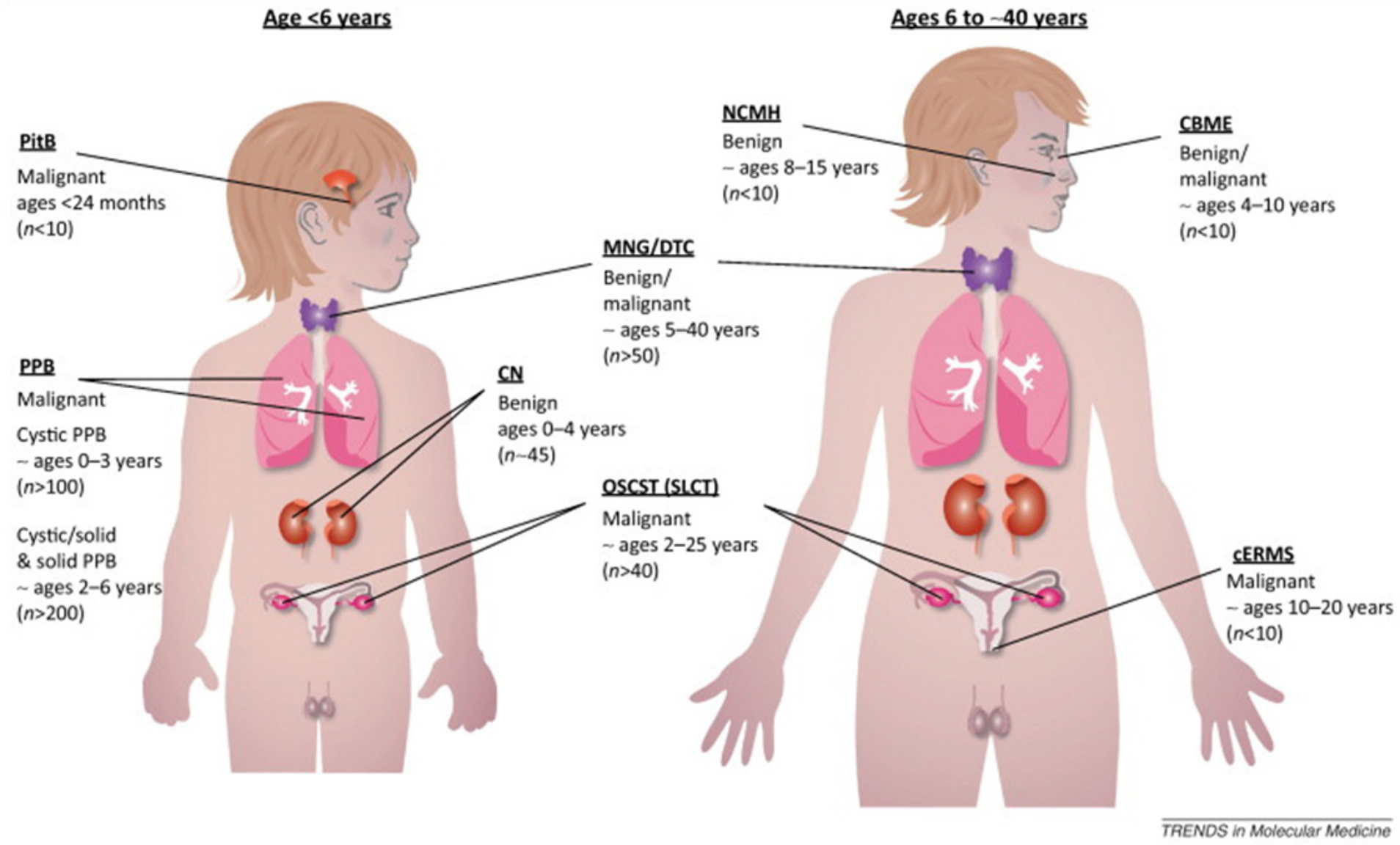
- Diagnosis:
  - Primary CNS DICER1-associated sarcoma
- Referral for consultation with the cancer predisposition program at DFCI
- Treatment: DFCI pleuropulmonary blastoma protocol
- The child is without evidence of recurrent disease after 1 year

DICER1 Tumor predisposition syndrome

- Autosomal dominant inheritance
- Two hit mechanism in DICER1-derived tumorigenesis:
  - Frameshift or splice germline mutation
  - Missense somatic mutation







TRENDS in Molecular Medicine

Interesting facts about this case

- Our patient does not have a DICER1 germline variant
- The pathogenic mechanism is similar to the one described in DICER1 syndrome-associated tumors
- The histology predicted the molecular results (at least for one reviewer)
- A primary intracranial DICER1 sarcoma has not been described yet
- Index case that prompted a search in our archives and identification of 12 other cases with similar histology and immunoprofile.

Thank you